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THE CONJUNCTIVAL TEST AS A GUIDE TO CLINICAL IMMUNITY IN HAY FEVER

MARY HEWITT LOVELESS, M.D.
New York, New York

THERE is at present no criterion by which the allergist assesses, in advance of the season of pollination, the adequacy of his specific therapy against hay fever. If such a yardstick were available, injections could be adjusted to the individual's needs instead of being given on an empirical basis.

Previous studies have suggested that the clinical improvement which is noted in pollen-sensitive patients after a series of injections may be related, at least in part, to the development of thermostable antibodies in their blood[3] and allergic tissues.[2] It appears that these bodies raise the local tolerance by binding the pollen antigen. If this theory is correct, then determining the state of susceptibility of the eye just prior to the season should give a clue to the probable behavior of the patient during the time of pollination. It was the purpose of the present investigation to test this possibility.

MATERIAL AND METHODS

Patients.—Ninety-five individuals were observed during 1943 and 1944, forty-four of them being studied during the two years. Comparison was made between the threshold of conjunctival reaction found at the onset of the season and the degree of clinical refractoriness subsequently noted while ragweed was in bloom. There were 139 such sets of data available for the group. All members gave typical histories of autumnal hay fever and showed the characteristic responses when tested by intracutaneous, conjunctival, nasal and passive sensitization techniques. Just prior to the conjunctival tests, a course of treatment with ragweed

From The New York Hospital and the Department of Medicine, Cornell University Medical College, New York, N. Y.
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extract had been given each patient. In thirty instances, this was the subject's first course. For all others, it was a booster course which consisted in many cases of a total of 10,000 protein nitrogen units administered in seven injections.

Antigen—Ether-defatted pollen was extracted for twenty-four hours in Coca's alkaline saline solution. The solutions were standardized on the basis of their phosphotungstic-acid-precipitable nitrogen. In order to minimize the aging of the antigen, one large batch was frozen and dried for all the 1943 experiments so that samples could be freshly dissolved every few weeks; and new extracts were prepared every other week during the 1944 studies.

Conjunctival Tests.—The patient was seated facing the source of daylight. The tester stood about four feet in front of the subject in order to judge the color of the conjunctivae and especially of the caruncles. One eye was used for the test, the other serving as control. The test dose was one fully-rounded drop, hanging from a 26-gauge hypodermic needle (Vim). The drop was brought upward in front of the cheek with the needlepoint directed *away* from the orbit. The drop was gently touched onto the everted lower lid at the moment the patient was asked to look upward at some object (to prevent blinking).

The initial strengths used were so dilute as to cause no reaction. Each five minutes more concentrated antigen was introduced until the first signs of reddening of the caruncle appeared. This was recorded as the threshold dose. Stronger solutions were then used until decided irritation and itching occurred, in confirmation of the threshold response. The sac was then flooded with physiological saline solution, and a few drops of epinephrin 1:1000 finally instilled. Tests, performed before a course of therapy, had been initiated with extract containing 1 P.N. unit per c.c. and carried on with 10-unit, 25, 50, 100, 150, 200, 300-unit solution or stronger until the first reaction point had been located and passed. After the course, the test was repeated in the other eye, commencing with the strength just below that which had provoked the threshold response formerly.

As a preliminary investigation into the reliability of the test, thirty-two individuals of the group were subjected to a second test which was carried out in the same eye two weeks later by a different tester. It was felt that any influence of a preceding test would be detected by this procedure.

Estimating Clinical Immunity.—The patient was asked to judge the extent of his improvement by comparing his current season with those previous to treatment. As a check on this somewhat unreliable yardstick of clinical progress, each was required to keep a daily record of symptoms in terms of hours and of severity. Many of the members of the group had kept such records for us for several years.

TABLE I. THRESHOLD VALUE OBTAINED WHEN CONJUNCTIVAL TEST WAS REPEATED BY A SECOND OPERATOR AFTER AN INTERVAL OF TWO WEEKS

	Threshold Reaction of Conjunctiva			
Case	Initial Test (P.N. units)	Retest	Second Tester	Level of Second Threshold
1	10	1	ML	lower
2	5	5	ML	same
3	10	10	ML	same
4	10	25	ML	higher
5	25	15	ML	lower
6	25	5	HS	lower
7	25	10	ML	lower
8	25	15	HS	lower
9	25	25	ML	same
10	25	25	ML	same
11	25	25	HS	same
12	25	25	ML	same
13	25	100	ML	higher
14	25	25	ML	same
15	50	10	ML	lower
16	50	25	HS	lower
17	50	50	ML	same
18	50	10	HS	lower
19	50	50	HS	same
20	75	100	HS	higher
21	75	200	HS	higher
22	75	50	HS	lower
23	75	200	HS	higher
24	100	75	ML	lower
25	100	35	HS	lower
26	100	150	HS	higher
27	100	400	HS	higher
28	150	200	HS	higher
29	200	100	HS	lower
30	200	100	ML	lower
31	275	275	HS	same
32	350	275	ML	lower

POLLEN COUNTS

Pollen Count—The concentration of ragweed pollen grains in the air amounted to 1,356 per cubic yard when the daily figures for August and September of 1943 were totaled. The comparable count for 1944 was 1,702 whereas the average for fifteen years amounted to 1,756. These data are based on slides which had been set out in the New York Meteorological Observatory of Central Park by Mr. David Morris, of the U. S. Weather Bureau, and which were analyzed by Mr. O. C. Durham.

Table I shows the conjunctival thresholds determined independently by two different operators when patients were retested after a two weeks' interval. Half the group were given the initial test by one worker, while the remaining sixteen cases were first examined by the other. It will be seen that the duplicate studies brought comparable results in most instances, despite the fact that different extracts were used and that the same eye was tested on the two occasions. Table II indicates that the result of

TABLE II. LEVEL OF THRESHOLD REACTION DURING SECOND TEST

Tester	Higher than in 1st Test (No. cases)	Lower than in 1st Test (No. cases)	Same as in 1st Test (No. cases)
H.S.	6	7	3
M.L.	2	7	7
Total	8	14	10

TABLE III. RELATION BETWEEN THRESHOLD OF CONJUNCTIVAL RESPONSE AND CLINICAL RESULT
(139 Courses given in 1943 and 1944)

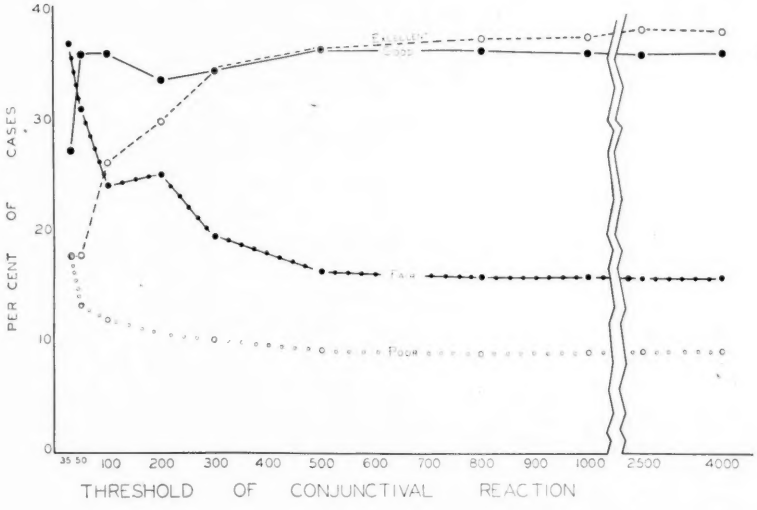
Threshold of Reaction in Conjunctiva after course (P.N. units)	CLINICAL RESULT			
	Excellent (90-100% relief) No. of Cases	Good (75-85%) No. of Cases	Fair (50-70%) No. of Cases	Poor (Less than 50%) No. of Cases
15		1		
25	2	2	3	1
35			1	1
50	2	5	3	1
75	2			
100	7	10	5	3
150	7	4	3	1
200	5	6	6	2
300	12	9		2
350	3	2		
400	4	5		1
450	2			
500	1	3		
600	1	1		
800	1			
1000	3	2	1	1
2500	1			
4000		1		
Total	53	51	22	13

the second test was identical with that of the first in ten cases, and was somewhat lower in fourteen others. The latter figure was partially counterbalanced by eight instances in which the second result was greater than the first. One can conclude from this experiment that the conjunctival test does not vary significantly with (a) two testers who have been trained to read in the same manner, (b) two successive extracts standardized similarly, or (c) a prior test performed on the same eye several weeks beforehand. It seemed possible that a test might lead to local immunity and thus falsely color the result of a subsequent one. This possibility can presumably be discarded for the technique employed, since 75 per cent of the group showed identical or slightly lower thresholds to retest.

Following their 139 courses of treatment in 1943 and 1944, our ninety-five patients were found to have conjunctival thresholds of reaction which ranged from 15 to 4,000 units, as indicated in Table III. The number

TABLE IV. PROPORTION OF CASES WITH SATISFACTORY CLINICAL IMPROVEMENT OCCURRING AT VARIOUS CONJUNCTIVAL THRESHOLDS

Conjunctival threshold (P.N. units)	Number of Cases with Satisfactory Result	Total number of Cases with this Threshold	Proportion of Cases with Satisfactory Result
35 or less	5	11	49%
50	7	11	63%
75, 100	19	27	70%
150, 200	22	34	65%
300	21	23	91%
350, 400, 450, 500	20	21	95%
600 to 4000	10	12	83%
Total	104	139	75%



of subjects reporting excellent, good, fair and poor clinical results in connection with these various thresholds is listed. It will be seen that most of the group could tolerate between 50-unit and 400-unit solution before showing visible irritation in their eyes, the greatest concentration of cases being in the vicinity of 100 to 300 units. Those thirty-five cases experiencing fair and poor improvement were found to have seasonal thresholds of less than 350 in all but three instances. The ratio of unsatisfactory to satisfactory result was one to each 2.3 cases for thresholds below 350; whereas, among patients with higher conjunctival resistance, the ratio was 1 to 10.

Table IV shows that the proportion of satisfactory to unsatisfactory clinical results increased from the low thresholds to the higher ones. In-

TABLE V. COMPARISON BETWEEN CONJUNCTIVAL THRESHOLD AND PERCENTAGE OF CASES WITH EXCELLENT OR GOOD CLINICAL RESULT

Threshold of Conjunctival Reaction	Number of Cases with Excellent or Good Result	Total number of Cases with this Threshold	Per Cent with Excellent or Good Result
35 or less	5	11	45.4
50 or less	12	22	54.5
75 or less	14	24	58.0
100 or less	34	49	62.6
150 or less	42	64	65.6
200 or less	53	83	63.8
300 or less	74	106	69.8
350 or less	79	111	71.1
400 or less	88	121	72.7
500 or less	94	127	74.0
600 or less	96	129	74.4
800 or less	97	130	74.6
1000 or less	102	137	74.4
2500 or less	103	128	74.6
4000 or less	103	139	74.1

dividuals whose eyes reacted to extract as dilute as 35 units per c.c. reported excellent or good relief in less than half of the instances. Among those whose thresholds lay in the region of 300 to 500, satisfactory results were obtained by over 90 per cent.

This tendency for clinical tolerance to rise with conjunctival tolerance can also be seen in the graph. Among the cases with thresholds of 35 or less, the incidence of excellent clinical response was two per eleven subjects, or 18 per cent. This same ratio applied for the 22 patients whose preseasonal thresholds were located at or below 50, 18 per cent of them experiencing almost complete loss of their hay fever. From this point on the graph, there is a sharp and steady increase in the proportion of cases with highly satisfactory clinical progress until at 300, 35 per cent of the accumulated patients from this and lower levels reported excellent control of their seasonal complaints. There was a slight improvement in the curve with still higher thresholds, but the number of cases added at these levels was small and the figures, therefore, are of less statistical significance.

Except for a preliminary peak in the region of 50 and 100, the curve for patients reporting a loss of three-quarters to 85 per cent of symptoms is similar to that of the above group. In contrast to these, the curves for patients with fair and with poor clinical results show a tendency to drop to lower levels as the related conjunctival threshold values rise.

If the curves for patients with excellent and good clinical results were combined, it would be found that satisfactory control of symptoms occurred in 45 per cent of cases with thresholds of 35 or less, in 63 per cent of those with thresholds of 100 or less, in 70 per cent of those with thresholds of 300 or less and in approximately 75 per cent of those whose oph-

thalmic responses were at 500 or below (Table V). Until this level was reached, therefore, the incidence of good results tended to be greater as the thresholds were higher.

DISCUSSION

In seeking an objective index to clinical immunity in hay fever, the author first investigated the serum antibodies. Although these thermostable, pollen-binding bodies are present in normal and in allergic individuals alike following their parenteral treatment with pollen extract and although their concentration appeared to vary with the clinical refractoriness of the patient[3], there are practical disadvantages to using the antibody titer as a guide to treatment. For one thing, the technique of passive sensitization is specialized, exacting and time-consuming. For another, the result obtained varies definitely with the choice of a normal test-subject. The number of comparisons must therefore be restricted. This makes it very difficult to determine *absolute* levels of humoral immunity and precludes the drawing of comparisons among sizable groups of individuals for the establishment of standards. The second objection may be overcome by the future development of the precipitin method of Hampton, Johnson, Alexander and Wilson.[1]

The conjunctival test does not carry these two disadvantages of the passive transfer technique. It is simple to perform, requiring no special training for the physician and no special equipment. It takes but a short time to complete. It is painless and safe providing simple precautions are taken. Since it is performed upon the patient himself and on one of the natural "shock" organs of hay fever, it should yield more accurate information than a test carried out in the skin of some test-subject. Furthermore, in assessing the pollen-binding power of a "post-treatment" serum, only one factor (namely, the thermostable antibody) is being studied whereas other important ones are disregarded. These other agents are the patient's reagins and other unknown "host" factors which undoubtedly play a role in the ultimate behavior of the allergic subject. Another point worth considering is the probability that the immune bodies which are circulating in the bloodstream play no immediate part in allergic manifestations. They are too remote from the portals of entry of the pollen in the eye and respiratory tract. The pollen antigen will have been combined with either the thermostable or the reaginic bodies in the tissues before reaching the circulation. Although it appears that a balance exists between the concentration of antibodies in the tissues and those in the bloodstream[3], this equilibrium might theoretically be disturbed at times and the antibody concentration of the serum might then be an unreliable index to the tissue immunity. It would seem wiser to test the tissue itself.

The tissue usually tested by allergists is the skin. Less constant and less valuable information has been obtained in the writer's hands with

skin-testing (even of the most controlled, threshold type) than with the conjunctival test[4], as will be shown in an early report. The nasal test has been found to yield more trustworthy data but has been associated with unpleasant after-effects.

The present study has indicated that the threshold test of the conjunctiva offers considerable promise as a guide to the state of immunity in pollinosis. Additional observations are being made during the current hay fever season. Although some members of our group experienced excellent results with relatively low thresholds of conjunctival reaction, the incidence of satisfactory clinical response appeared to be greater among patients with thresholds in the region of 300 to 500. Until more data are available, it will be our practice to treat the newly acquired patient with booster doses which will, if possible, bring his conjunctival threshold to these levels. Once he has been watched through a successful season, the related ophthalmic threshold noted during that season can serve as the goal for future therapy. By studying the eye at intervals during these future courses, it will be possible to ascertain what the minimal requirements in dosage are. Individualizing therapy in this way should tend to bring each patient optimal results in minimal time, avoiding both under- and overtreatment.

CONCLUSIONS

1. A modification of the conjunctival test, designed to reveal the threshold of reaction toward pollen extract, is described.

2. Preliminary studies indicated that the test varies unimportantly with the operator, with two extracts of the same pollen, and with an interval of a few weeks. A preceding test did not influence appreciably the threshold value found in a second test two weeks later.

3. Although some patients experienced successful seasons with conjunctival thresholds which were relatively low, in general, the clinical results were better as the thresholds were higher. Among ninety-five cases observed for one or two ragweed seasons, 95 per cent of those with thresholds of 350 to 500 reported good or excellent clinical results, whereas only 49 per cent of those with thresholds of 35 or less showed satisfactory clinical control of their hay fever. It would seem indicated to give newly acquired patients "booster" courses adequate to raise the thresholds to at least 300, if possible.

4. The conjunctival threshold test gives promise of serving as a guide to the amount of specific treatment required by the hay fever case. Average figures for the group may be useful as crude indices to the needs of the newly acquired patient, until such time as his own "protective" threshold can be established by the test of one or more seasons.

The writer wishes to express appreciation to Miss Helen Schneemann for technical assistance during these studies.

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MOLD ALLERGY
II. Clinical Analysis

GEORGE I. BLUMSTEIN, M.D.
Philadelphia, Pennsylvania

CONSIDERABLE controversy has existed regarding the incidence of mold allergy since van Leeuwen[12,13] first called attention to the important role that molds play in precipitating allergic symptoms. At first only sporadic reports of mold allergy appeared in the literature, but with the advent of Feinberg's[4] work, more extensive surveys began to appear. Most of these reports emanated from the midwest where mold allergy was more prevalent, or was recognized to a greater extent than in other parts of the country. This was at first attributed to the peculiar flora of the locality and the high concentrations of atmospheric mold spores, but it shortly became evident that mold allergy existed throughout the United States. The incidence given in each report, however, varied greatly, depending largely upon the locality in which the survey was made. The criteria for establishing a diagnosis of mold allergy likewise varied, making it difficult to correlate or compare the results.

Lamson and Rogers[7] report an incidence of 12.2 per cent positive skin tests in a series of 1,259 patients, but make no mention of the incidence of clinical sensitivity. Schonwald[11] reports 57 per cent positive skin reactions to molds in a series of 150 allergic patients, with 76.7 per cent improvement after adequate mold therapy. Pratt[9] reported over 25 per cent positive skin reactions in a group of 177 atopic children. Jimenez et al.[6] found seventeen mold-sensitive patients in a group of 292 allergic patients, an incidence of 5.8 per cent. Vander Veer[14] reports thirteen positive skin tests in a series of eighty allergic patients tested, an incidence of 16.25 per cent. Chobot et al.[3] reported an incidence of 26.5 per cent positive skin tests to Alternaria among an unselected group of 244 allergy patients. No attempt was made to determine the incidence of clinical sensitivity in this group although twelve out of twenty-eight selected patients were constitutionally sensitive. Pennington[8], in studying a group of 526 patients, found sixty-seven who presented a suggestive history of mold allergy. Provocative tests were done on sixty-one of these patients and only twenty-two were found positive. Thus twenty-two of a group of 526 patients (4.2 per cent) exhibited definite mold allergy.

The percentage of positive skin reactions in the above reports varies from 5.8 to 57, while clinical sensitivity varies from 4.2 to 42 per cent. These divergent results seemed too great to be reliable. They suggested dissimilar methods of investigation and lack of uniformity in the preparation of extracts and in the criteria for determining clinical sensitivity. The present study was undertaken in an effort to clarify this situation

From the Clinic of Allergy and Applied Immunology, Temple University Medical School and Allergy Clinic, Mt. Sinai Hospital, Philadelphia.

and also to search for the offending factors in patients with seasonal hay fever and asthma that were not attributable to any of the known airborne allergens in this locality.

PROCEDURE

Thirteen known mold cultures were selected either because of reports of clinical sensitivity to them in the literature, or because of the relative frequency with which they were found on our exposed slides and plates. Each of these was subcultured in a 500 c.c. Erlenmeyer flask containing between 50 and 75 c.c. of a broth made up as follows:[5]

Distilled water	5,000 c.c.	Sodium chloride	25 Gm.
Peptone (Armour)	50 Gm.	Meat Extract (Armour)	25 Gm.

Autoclave. Filter. Add maltose 100 Gm. Autoclave in large flasks.

Maximum growth was attained in three weeks. The mold pellicle was then removed and placed in a Bard-Parker sterilizing jar over 40 per cent formalin for twenty-four to forty-eight hours. This killed all the molds and permitted us to work with extracts of dead organisms. The material was air-dried and ground into a fine powder from which was prepared a 3 per cent extract of mold powder in Coca's solution.* Nitrogen determinations were done on all extracts and for testing purposes they were diluted so as to contain .1 mg. Total N per cubic centimeter.

All patients attending the allergy clinic were tested with these materials. This assured us of a heterogenous group of thoroughly studied allergic patients. All patients exhibiting positive skin reactions to the mold extracts were then tested by the nasal route with the corresponding mold powder. If it could be proved that the powders used were nonirritating, then any resulting reaction could be attributed to specific sensitivity. Blood was obtained from each reactor and passive transfer tests done to demonstrate the presence or absence of sensitizing antibodies. Patient's symptoms were then correlated with the atmospheric mold concentration. Other things being equal, a direct relationship should have existed between the severity of symptoms due to mold allergy and the atmospheric mold concentration.

RESULTS

Four hundred six allergic patients were thus studied. One hundred sixty-nine displayed positive skin reactions to one or more mold extracts, an incidence of 41 per cent. Table I shows the frequency with which each mold reacted, and the degree of reactivity.

*Na Cl 0.5 per cent
Na HCO^3 0.275 per cent
Phenol 0.4 per cent

It will be noted that the majority of the skin reactions were only slightly positive (+). As will be shown later, a large proportion of these reactions were nonspecific and therefore of no clinical significance. When of greater intensity, they were just as pronounced as those seen in cases

TABLE I. FREQUENCY AND INTENSITY OF SKIN REACTIONS TO MOLD EXTRACTS

Degree of Reaction	+	++	+++
Alternaria	21	12	8
Aspergillus flavus	15	1	0
Aspergillus fumigatus	11	0	0
Cephalosporium	38	6	0
Fusarium	20	0	0
Helminthosporium	22	4	0
Hormodendrum	19	3	3
Monilia sitophilia	25	6	2
Mucor	35	3	2
Penicillium digitalus	21	4	0
Rhizopus	17	3	0
Torula	15	3	0
Trichophyton	22	1	0

of pollinosis. The most frequent skin reactors were Alternaria, Monilia, Hormodendrum, Mucor, Cephalosporium, Helminthosporium, Penicillium, Rhizopus, Torula, Trichophyton and Aspergillus flavus, being named in the order of importance.

Each subject yielding positive skin reactions was further tested by the nasal route.[1] The mold powder used in each case corresponded to the extract producing the positive skin reaction. A positive reaction consisted in the precipitation of hay fever or asthma-like symptoms similar to those complained of by the patient. Such a reaction was regarded as specific and indicated the presence of clinical sensitivity unless it occurred in patients with a hyperesthetic rhinitis. The inhalation of any particulate substance in the latter type is followed by a rhinitis of nonspecific character. Twelve patients showed positive reactions to the inhalation of various mold powders. Table II depicts the number and the various types of patients tested, the number of positive skin reactions and the percentage of clinically sensitive patients in each group.

Thus of 406 patients studied, 169 (41 per cent) gave positive skin reactions, while only twelve (3 per cent) displayed clinical sensitivity. It will be noted that all cases of mold allergy occurred in patients with seasonal symptoms, accounting for twelve of 133 cases, an incidence of 9 per cent.

An effort was then made to determine the existence of any special clinical features that might aid in its clinical recognition. A review of the histories of these twelve patients revealed the fact that ten presented symptoms of asthma while the remaining two complained only of seasonal rhinitis. In the group as a whole, itching of the eyes was a minor com-

TABLE II. DISTRIBUTION OF MOLD SENSITIVITY AMONG VARIOUS TYPES OF CLINICAL ALLERGY

	No. of Patients	Positive Skin Reactors	Clinical Sensitivity
Seasonal hay fever	121	66	2
Perennial hay fever	80	31	0
Seasonal asthma	12	11	10
Perennial asthma	158	51	0
Urticaria, eczema, migraine, contact dermatitis, vernal conjunctivitis	35	10	0
	406	169 (41%)	12 (3%)

plaint, a differential point that might aid in distinguishing it from pollen hay fever where this is a rather constant and annoying symptom. Another aid in the differentiation of mold allergy from pollinosis was found in the duration of their symptoms. The patients with mold allergy had active clinical symptoms without remission during the period of sporulation, that is, from May to November.[2] A symptom period of this type could not be explained by the pollination of any group of plants, for there invariably is a remission of symptoms between the grass and weed seasons (late July and early August). Many of the patients in this group had previously been treated unsuccessfully with various mixtures of pollen extracts.

Multiple clinical mold sensitivity existed in seven of the twelve cases. The offending molds in their order of importance are Alternaria (10), Hormodendrum (5), Monilia (3), Helminthosporium (2), and Mucor (1). Three of the twelve patients gave specific positive nasal tests with each of the thirteen mold powders tested. Reactions of this type may have been due to some irritating substance derived from the culture material and therefore common to all the powdered extracts. Positive nasal reactions were obtained in these individuals by agitating petri dishes containing agar cultures of each of the molds in question. The spores were thus liberated without an admixture of culture material and disproved the above concept. A satisfactory explanation for this phenomenon is still lacking.

The frequency of an associated pollen factor in eight of the twelve patients serves to call attention to the multiple allergens that may act as contributing factors in seasonal allergies.

Passive transfer tests with the serum of ten of the twelve clinically sensitive patients yielded positive tests for the presence of sensitizing antibodies. These sensitizing antibodies were specific for each mold and the reaction to one mold extract could not be obliterated by neutralization or exhaustion by the previous addition of another.

DISCUSSION

Mold allergy occurred in 3 per cent of 406 allergy patients in this series, or in 9 per cent of the seasonal cases. This should tend to place

the main emphasis on the pollens as the cause of seasonal allergies and reserve a secondary role for the less frequent mold factors. Mold allergy should be suspected in patients presenting seasonal variations in symptoms that are not attributable to the usual seasonal pollen factors.

The clinical symptomatology varies with the individual patient but differs sufficiently from cases of pollinosis to be of clinical value. Complaints referable to the eyes were minimal in most cases and could be elicited only with great difficulty. This differs from pollinosis where eye symptoms are prominent and quite annoying. Nasal symptoms, although present in each of the twelve patients, constituted the chief complaint in only two. The remaining ten suffered with seasonal asthma. The period of suffering in mold allergy does not correspond with the pollinating period of any pollen or group of pollens. Symptoms are most severe, as a rule, in July and August, when the pollen concentration in the air is lowest and the spore count highest. There is no period of remission in mold allergy such as occurs in pollen allergy between the grass and weed seasons. Thus, mold allergy may be suspected clinically in individuals presenting themselves with seasonal, unremitting symptoms, especially asthma, that do not correspond with the pollinating period of any group of pollens.

The skin tests in clinically sensitive patients were just as definite and specific as occurred with pollen in cases of hay fever. Mold extracts should not be used routinely for skin testing because of the low incidence of sensitivity in the allergy group as a whole. Its use is indicated in those cases of seasonal allergy that are not due to pollen, or those cases of pollinosis where a complicating mold allergy may co-exist and be responsible for poor therapeutic results. It is not necessary to test with all the molds used in this study. The extracts suggested for skin testing are those that have been found capable of producing clinical symptoms and include Alternaria, Hormodendrum, Monilia, Helminthosporium, Cephalosporium and Mucor.

As already indicated, the reason for such divergent percentages of clinically sensitive cases in the available reports depends upon two factors: first, the locality in which the survey was made, and secondly, the lack of uniform criteria for judging clinical sensitivity. Increases in the atmospheric pollen or mold concentration has never influenced the percentage of sensitive patients in a given locality and could not explain the variability in clinical sensitivity. A more likely explanation would seem to be the failure on the part of investigators to utilize a simple, objective test for the determination of clinical sensitivity. The nasal test fulfills these requirements and was the provocative test used in this study. A patient was said to be clinically sensitive when the history corresponded to the period of sporulation and when positive skin and nasal tests were obtained. Some patients previously classified as pollen allergics with negative skin and nasal tests were properly categorized as cases of mold al-

lergy. Considerable skepticism should be cast upon the etiologic diagnosis of seasonal syndromes with negative skin and clinical tests. The offending agent in each instance should reproduce the symptoms exhibited by the patient.

The results of treatment with the appropriate mold extracts yielded uniformly good results. The failures encountered were in the same ratio as occurred in cases of pollinosis. Constitutional reactions were far more frequent in this series of patients than in a similar group with pollen allergy. This could be due to the lack of standardization of the mold extracts. No standard method for the preparation of mold extracts has been agreed upon. Pratt[10] has shown that the spores contain the allergen in much greater concentration than do the mycelia. His method of brushing the spores off petri dishes with a camel's hair brush has been found wanting for the yield was extremely small despite the use of dozens of petri dishes. The broth method of culture used in this experiment yielded a predominate growth of mycelia. Extracts prepared by both of these methods were actively allergenic when tested on sensitive patients. In an effort to imitate pollen collection and to have a standard parent substance from which extracts could be prepared, attempts were made to collect the spores directly from the host on which it grew. This procedure was finally abandoned because of the negligible yield and the difficulties encountered in determining the type of spore at the site of collection.

Other problems encountered during the course of this investigation warrant discussion. One of them is the occurrence of seasonal asthma in a small group of patients that could not be explained by any known air-borne allergen. Their season began in early to mid July and subsided by mid September. Clinically they resembled cases of mold allergy because of the paucity of hay-fever-like symptoms and the preponderance of asthmatic symptoms. The etiology of this group of patients remains to be determined.

Another difficulty was the lack of a competent mycologist with sufficient time to aid in the identification of mold cultures. Many plates were undiagnosed because of this deficiency. Many spores found on exposed slides failed to grow on a variety of culture media. The nature, origin and importance of these spores might be determined if a full-time mycologist was assigned to the problem. Knowledge of this sort might also aid in establishing the etiology of many seasonal asthmas now classified as "of unknown origin."

SUMMARY

1. Forty-one per cent of 406 thoroughly studied allergic individuals in this series displayed positive skin reactions to one or more of the thirteen mold extracts used in this study.

2. Twelve clinically sensitive mold subjects were found in this group—3 per cent of the entire group or 9 per cent of the seasonal group.

3. All these patients presented histories of seasonal allergies corresponding to the period of greatest mold concentration in the air. Ten of the twelve patients suffered from asthma, while eight manifested some type of pollen sensitivity in addition to their mold sensitivity.

4. A provocative test, in this case the nasal test, was used as an adjuvant in determining clinical sensitivity.

5. The only molds of etiologic significance in this study were Alternaria, Hormodendrum, Monilia, Helminthosporium, Cephalosporium, and Mucor, named in their order of importance. It is suggested that extracts of above be used for skin testing in patients suspected of being mold-sensitive.

6. Mold allergy may serve partly to explain the origin of many seasonal cases of hay fever and asthma that were previously considered to be cases of pollinosis with negative skin and clinical tests.

1614 Locust Street

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The Experimental Use of Ethylene Disulfonate (Allergosil Brand) in the Prevention of Anaphylaxis in Guinea Pigs. Fish, R. T., Small, W. S., and Foord, A. G.: J. Allergy, 15:14, 1944.

Powdered egg albumin was used for sensitizing eighty-nine guinea pigs in four experiments. Thirty-three pigs "protected" with an injection of ethylene disulfonate showed a mortality rate of 60.61 per cent subsequent to shock dose, thirty-one pigs "protected" with an injection of water showed a mortality rate of 67.74 per cent. 25 untreated pigs showed a mortality rate of 72.00 per cent. Mathematically, the observed differences are within limits of standard error and chance. Conclusion reached was that ethylene disulfonate did not produce a significant degree of protection against anaphylactic shock.

THE ORGANIC STATE IN THE PROBLEM OF ALLERGY

WILLIAM F. PETERSEN, M.D., F.A.C.A. (Hon.)
Chicago, Illinois

THE allergic reaction of the tissues is reaction to a stimulus differing from the normal only in its speed and its intensity. It is a purposeful reaction—a reaction against the unusual or foreign. It is a reaction that involves the vascular tissues—the endothelium—the vessel coats—and, in so doing, the common clinical expressons elicited reflect rapid shifts in capillary permeability—rapid change in the tone of smooth musculature.

If in our study of the allergic reaction we are wholly preoccupied with the specific allergen (the effector) and are only incidentally concerned with the state of the effected tissues we will be confronted with inexplicable situations and paradoxical phenomena. Yet that is precisely what does happen in allergy and is precisely what happened for many years in the field of bacteriology and immunology.

As in all biological phenomena we have proceeded on the assumption that the organic reactions are simple and that the cause is single. Henderson[2] pointed out:

"There are certain deficiencies of the medical sciences to which little attention has been devoted. These deficiencies depend upon the fact that living organisms are immensely complex and that the experimental sciences, by hook or by crook, analyze the concrete reality into relatively simple elements. But the complex reality is never describable by merely adding up these elements, for they exist in a state of equally complex interaction. * * *

"When men reason deductively about the complex affairs of everyday life, they nearly always leave out something, or rather many things, both things they forget and things they don't know. More often than not their conclusions are therefore unsound. This is what Whitehead calls 'the fallacy of misplaced concreteness.'"

"The fallacy of misplaced concreteness is very common in the form of arguments involving 'other things being equal.' In general, it may be said that all arguments involving such notions as other things being equal, or *pari passu,* are probably fallacious.

"The medical sciences have suffered and continue to suffer from this fallacy. The rise of bacteriology and its influence upon medical thought and practice may be taken as an example. About the time of Pasteur's first discoveries, the thought of Claude Bernard and of other physiologists seem to indicate a movement toward the study of the interrelations between many things and a recognition of this kind of study, synthetic physiology, as one of the foundations of the medical sciences and as the source of an indispensable point of view in all kinds of medical work. The discovery of specific pathogenic microorganisms to have led back to an over simplification of thought about the origin and nature of disease. For some time at least, the tendency was to think of diseases as entities hardly less definite than atoms of oxygen or molecules or hemoglobin. Let us recall the fact that even hemoglobin *in situ* is not a single definite thing. The disposition was even more marked to think of the specific organism as the cause—the sole cause—of a specific disease, and later to think of the specific antitoxin as the specific cure of that dis-

ease. Similarly simple views of nutrition have prevailed. There was the epoch of calories; we now live in the epoch of vitamins. Hormones also are now having their day, and excess or deficiency of specific hormones, like excess or deficiency of particular vitamins, is often thought of as the cause of a specific disease."

So, too in allergy!

In the field of allergy, we tacitly assume that the subject's reaction to the allergen should be alike from day to day. Actually the organic state of the subject is never the same from day to day. But if reactivity varies, the reaction to an allergen will vary. It is this problem that will be discussed in the papers that follow.

The individual cell of the body exists in a state of unstable equilibrium —pendulating between two poles—activity and rest. We speak of this as the normal biotonus. Deviation from the normal biotonus in the direction of increased catabolism ("stimulation," increased oxidation, et cetera) may lead to fatigue and to death. Deviation in the opposite direction leads through inhibition (sleep) to a state of arrest that may persist for long periods of time but which usually ends in erosion. In the human, an integrated community of some eighteen or twenty billion cells, large numbers of individual cells can and do proceed through fatigue and to death without clinical reflection. The labile biotonus of the whole organism is maintained by the interplay of many individual checks and balances—for instance, the acid base balance, the water balance, the endocrine balance, the temperature balance, the lipoid balance, the calcium potassium balance, the ferment-antiferment balance—to mention but some of them.

Every energy impact upon the body must be equilibrated and the energy effectors are legion. The most common are changes in the immediate environment in which we exist—changes in light, in the air (temperature, humidity, electrical potential, et cetera), the cumulative effect of season, the character of food, work and exercise, the social mileau, the contact with the world of micro-organisms and allergens and toxins.

For the allergist the rôle of season is of great importance. Not only because of the seasonal tide of exposure to the botanical allergins (that we will ignore for the time being); *because the organic state of the patient is greatly modified with season!* But before entering into the details of this phase of the problem I shall first turn to examine a few of the simplest criteria that we can use in observing normal and abnormal biotonus pendulation in the human.

At the root of all *dis-ease* is air hunger. As long as cells are adequately supplied with oxygen, we have little dysfunction. Even the acute clinical picture in the various allergic manifestations is basically associated with local anoxia—brought about with changing tone of smooth muscle (spasm) or by changes in cell permeability and the coincident stasis that is thereby entailed.

It requires no elaborate apparatus to follow the state of the normal

biotonus of the body as reflected in air hunger. We can make use of a simple breath-holding test. This, when determined at the same time of the day in day-by-day sequence, will provide an excellent criterion of the organic state.

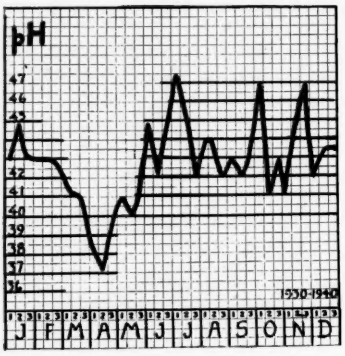

Fig. 1. Curve of pH levels of the venous blood of the arm, made in day-by-day fashion for the period 1930-1940. Note the characteristic lowering of level to its April decline to relative acidity and the sharp increase in summer and autumn.

We can use the blood pressure in a similar manner. Or any other test that we may wish to employ—the pH, the sugar level, the skin reaction the dark adaptation of the eye, the circumference of the leg or the ability of the subject to suspend his body from a bar.

SEASON

We will return to the effect of season, using blood pH as a criterion. The curve of the mean annual blood pH curve from our human material for the decade 1931-1942 is illustrated in Figure 1. The pH declines to a low level in April; in the summer and autumn this is reversed. This is a basic biochemical tide that will find reflection in every physiological and pathophysiological reaction pattern.

If for instance we take blood pressure readings (Fig. 2) at the same time each day in an old woman (with vascular sclerosis) living quietly in a hospital ward, with no alteration of environment other than that associated with weather, it will be noted that there are wide changes from day to day. For instance, pressure may reach 240-250 on some days, on others 150. The seasonal tide is well defined. In the summer the pressures are lower (peripheral dilatation) (*S*), rising in the autumn (*A*) to a crest late in December. Then in January there is an abrupt decline (*J*). But while the decline in summer was a normal response to an environmental situation when peripheral vessels dilated with warm weather (*S*), the decline in January was the result of a totally different mechanism. The great pressor crests in December resulted in anoxia, the production

Fig. 2. Daily systolic and diastolic blood pressure readings on subject M., May, 1934, to May, 1935.

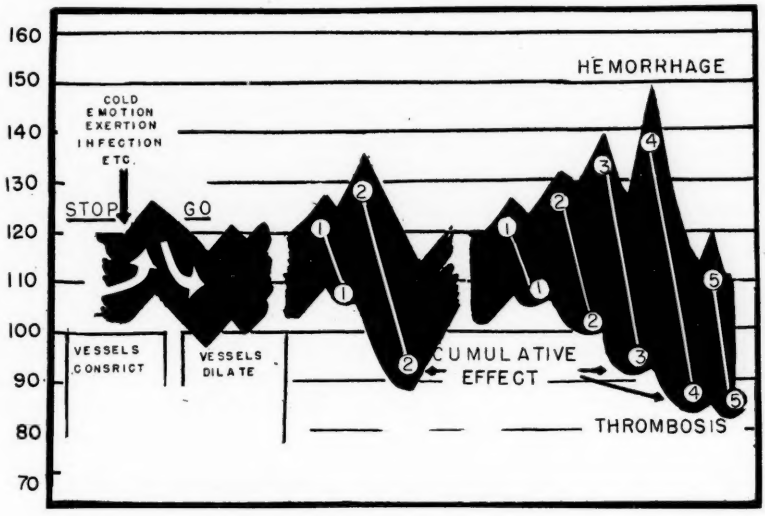

Fig. 3. Schematic reaction pattern.

of capillary active substances and the vascular tissues (smooth muscle, endothelium) became fatigued. But these are seasonal effects—their import for the allergic reaction might seem obvious.

A Schematic Illustration.—This organic rhythm can be illustrated very simply if we merely diagram blood pressure levels, as in Figure 3. At the arrow an energy impact occurs—it may be cold, an emotional upset, exertion, infection, an allergen. A sympaticotonia follows—vessels constrict, pressures rise—it is an "alert" or an "adrenal" phase, if you so wish to designate it. Selye termed it the "alarm reaction."

If at this time the skin is tested, flares are negligible; there is greater resistance to infection—cells are temporarily less permeable. A relative alkalosis and hyperglycemia exist, together with an increase in blood pressure.

This "adrenal" or "stop" phase goes over to the "go" phase—vessels

dilate—there is relative acidity—cells become more permeable—they are less resistant to injury—skin flares are exaggerated.

All this is very simple. Assume now that we must equilibrate two such impacts in rapid succession *(1 and 2 in the central diagram)*. Then the pressor level will be higher and also lower, and if after *(2)* another factor, such as undue heat supervenes, then the pressure may fall to unusually low levels. Or, if with seasonal accentuation, a series of impacts supervene in rapid succession, then we will face the situation in the third diagram—with periods of great pressure crests and depressions in close sequence.

What has been illustrated here for blood pressure holds for every component in the complex series of organic balances.

Allergic phenomena are characterized by sudden changes in the state of the circulation. With this come local sensory phenomena (itching, flushing and pain), then effusion and swelling, then the general expression of disturbance in the blood distribution between the skin and the splanchnic area. Primarily the effect is on the capillary endothelium—then the associated changes in the autonomic (endocrine—nervous—chemical) tone—with reflections in the major organs—stomach, liver, kidney, spleen, the bone marrow, et cetera.

If an allergic reaction takes place when the organism is in the phase of a low pH (the winter-spring status), with the implication of stimulation or fatigue—with buffers exhausted, calcium and lipoids depleted, blood pressures low, it is but logical to expect that reactions that involve capillary permeability will be accentuated. The autumn status may reverse the picture and lessen the allergic reaction that depends on the capillary mechanism.

If, on the other hand, the particular allergic manifestation involves undue smooth muscle contraction (vascular spasm, or spasm of the bronchus or the gut) then we will find a reversal of this seasonal picture—such allergic phenomena will tend to be accentuated in the summer and autumn and diminished in the spring.

And if, in the allergic mechanism, both mechanisms are involved (that is, an interplay of changing vascular permeability, together with smooth muscle relaxation and spasm) symptoms may be accentuated "at the change of the seasons"—that is, in the spring and autumn. This is by no means an uncommon phenomenon in the allergic states not directly associated with the pollens. This effect of season in altering the "state" of the organism becomes dramatically apparent in asthma, in tuberculosis, in ulcer, in migraine, et cetera.

Keeping this seasonal pendulation in mind we must extend our survey to include shorter disturbance of the balance, as well as longer cycles that will extend over the years. Shorter disturbances are commonly the reflection of air mass change—of weather. These air waves set up organic pendulations that may be of short duration, but of great amplitude. There

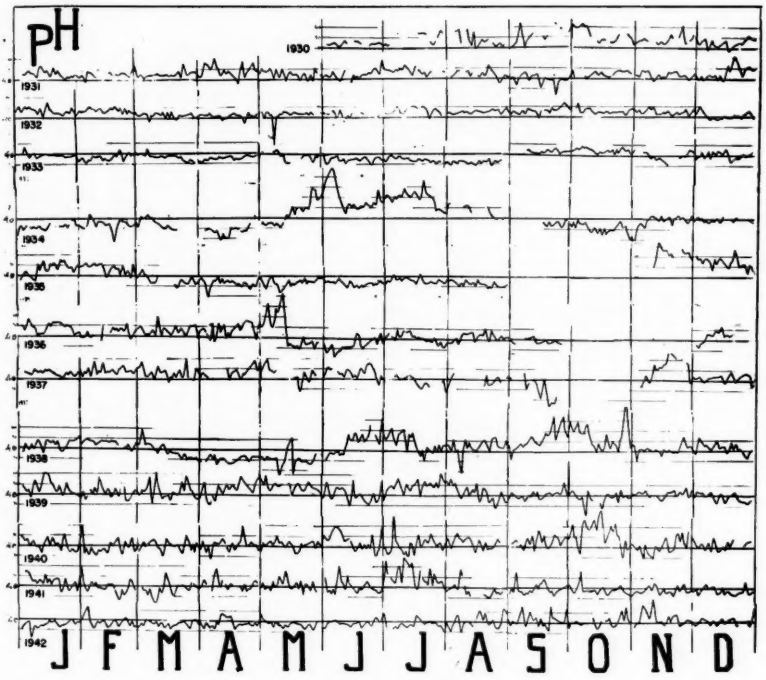

Fig. 4. Blood pH levels, 1931-1942.

is a diurnal cycle; there are cycles of a week, and longer cycles that are related either to the lunar period, or to the solar day (i. e., the rotation period of the sun), as well as the long climatic cycles that may be related to sunspot periodicity or to the amplification of such rhythms.

If we determine the pH levels for the period 1931-1942 (Fig. 4), there is indication that a long range chemical cycle of this type does occur in the human population. For the allergist this would mean that allergic responses would differ in certain years—the vegetation (and so the dosage of allergenic agents) will also differ with such climatic cycles.

The graphs present day-by-day determinations of blood pH levels of from three to five patients each day (normal or ill with relatively minor disturbance). Note the relative stability of the curves in 1932-1933 (a period of least solar disturbance) and the wide deviation in the years that follow. In 1934, for instance, an alkalotic peak occurred with the great drought and heat period (May and June). In 1936, we have an opposite situation—an alkalotic crest in early May, followed by a sharp decline in the latter part of May and June. Each year reveals a pattern of its own.

Obviously, an allergen in contact with sensitized tissue in early June, 1934, will elicit a different reaction than when in contact with the same

tissue in June, 1936. But such wide swings may occur in short intervals, as becomes evident in examining the graph.

The allergist is quite well aware of this change in the status as it affects his skin-testing methods. On some days all of the reaction flares and wheals will be large—on other days negligible. In the parlance of practice he deals with a "hot" skin or a "cold" skin. And that is a true evaluation, for at certain times the smooth muscle of the peripheral vessel is in a spastic state and vessels will not dilate—at other times will dilate readily. But he is apt to forget that it is not only true of his skin testing—it is a criterion of what is going on at the focus of clinical disturbances! The "organic state" is never the same, even if the dosage and character of the impact (in this case the allergen) is the same.

Before proceeding I would stress one more point. The allergic reaction, involving cellular responses that are also called into play by nonspecific energy impacts (from which they differ mainly in speed and amplitude of response) can precipitate clinical pictures that are identical with those due to a wide variety of other forces that cause autonomic dysequilibration, for instance, an appendicitis, a colitis, a paroxismal tachycardia, a coronary episode, a migraine. But that does not justify the myopic assumption that every appendicitis, every colitis, every tachycardia or coronary spasm or migraine has its origin in a specific allergic reaction.

The allergist must be a physician who evaluates his special field in the much wider framework of the general principles of reaction to environment, not merely reaction to a specific allergen, with disregard of all other effectors. I would again refer to Henderson's paper in which he traced the same fallacy during the bacteriological era. It was a period of oversimplification. Bacteria plus human spelled disease. Today we know that bacteria plus the kind of human—plus the state of the human (and that means time and place—food and work—sunshine and weather—season—sex) present an equation which may mean disease. A similar situation holds true for the allergic factor in disease.

Doctor Dutton has published an interesting study in which he incriminates an allergic factor in the onset of appendicitis. I am of the opinion that an allergic factor may play a rôle in appendicitis. But that by no means implies that specific allergy is *the* cause of appendicitis. Years ago we ascribed the cause to bacteria. Of course, bacteria invade the wall of the appendix, but those self-same bacteria were in and about the appendix for years and no appendicitis occurred until the "state of the tissues" was so changed that bacteria could invade. An allergic disturbance of the autonomic equilibrium can so change the state of the organism that the appendix may become the seat of inflammation, but any other major energy impact can bring about a similar situation—heat or cold, emotional or physical trauma, an infection, an intoxication, a sudden endocrine unbalance.

Inasmuch as this organic tide is (1) a factor in the precipitation of all clinical episodes and (2) uniform in its character, irrespective of the particular energy impact that has brought it into play (temperature change—emotion—trauma—allergen, et cetera) it will be useful to present a detailed examination of the more obvious manifestations.

The primary effector in all tissue regulation is air hunger and was so recognized by the Greeks. Air hunger occurs when there is vasoconstriction (*i. e.,* a phase of smooth muscle contraction) or vasodilitation (a phase of capillary dilitation and stasis). Hippocrates put it succintly, "So in one place it stops, in another it passes sluggishly, in another more quickly. The progress of the blood through the body proving irregular, all kinds of irregularities occur."

The organic tide that I have been discussing is the reflection of this changing oxygen potential. At some times the body is air hungry, at other times has a relative oxygen plethora. In the simplest of fashions we can determine this by merely determining the breath-holding time. When taken each day at the same time it provides us with an excellent criterion of the organic state. How useful, I can best illustrate by the observations in the following case.

THE ORGANIC TIDE OF ANOXIA

Thrombosis occurs when the blood pressure is low, the current sluggish, the vessels adhesive and the clotting time shortened. At present more than one-third of all doctors die from coronary thrombosis, a proportion that will increase.

Coronary thrombosis is a reflection of the organic pendulation or tide that I have been discussing.

The organism first passes through a period of *increased vascular tone.* This is most commonly associated with undue environmental cold, often with increased activity, excitement, trauma, et cetera. During this phase the tissues become relatively air hungry. Capillary active substances are then formed (histamine and histamine-like substances, intermediary acid products of anoxiobiosis, carbon dioxide, et cetera), which all lower the blood pressure level and dilate the capillaries. With this the phase of increase in blood pressure shifts to one of lower blood pressure. Capillary and venous endothelium become more adhesive; the clotting time is shortened. This transition from high to low pressure may occur in a very short time (one or two days) or may reach its maximum in the course of ten days.

Now, if in this organic state of relative acidosis, of lower vascular tone, of shortened coagulation time, an environmental situation develops which would further lessen vascular tone (sudden warm weather or a mental depression or physical fatigue) then pressure levels may sink to critically low levels in regions of the body where vessels are unduly adhesive and during a time when coagulation is accelerated—then coronary thrombosis!

H. I., pharmacist by training, scientist by aptitude, allergist by preoccupation, suffered from a clinically well-defined coronary thrombosis on September 18, 1942.

Let us look at the record in this case. Figure 5 illustrates merely the maximum and minimum temperatures of the time in silhouette, the barometric pressure in

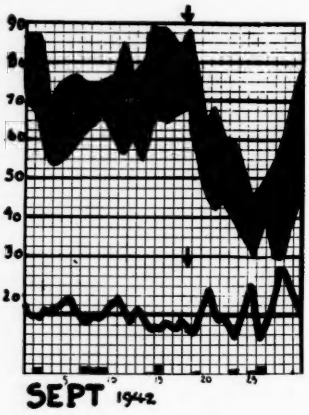

Fig. 5. Meteorogram, Chicago, 1942. Upper Curve—Maximal and minimal daily temperatures. Lower Curve—Barometric pressure. Arrow—Day of coronary attack.

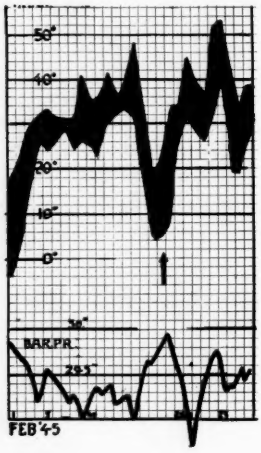

Fig. 7. Meteorogram, February, 1945. Arrow—Death.

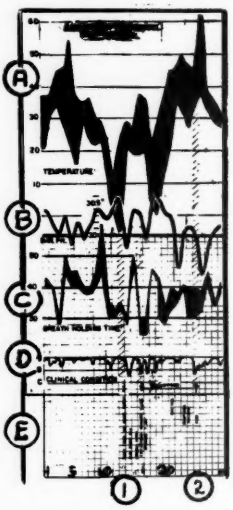

Fig. 6. February, 1944. Curve *A*.—Daily maximum and minimum temperatures. Curve *B*.—Barometric pressure. Curve *C*.—Breath-holding time. Curve *D*.—Subjective state. Curve *E*.—Illness notes of S. G. (1) Illness (virus pneumonia) began. (2) Death.

heavy trace and rainfall in black bars at the date line. It will be observed that it had been hot at the beginning of the month, then followed two periods of relative cold (the last on the 13th), then a sudden shift to high temperatures. With the final heat crest on the 19th (temperature 88°, barometric pressure lowered) the subject developed his coronary attack. In addition to the reaction demanded by

the changing physical environment, he was mentally depressed at the time. He made a fair recovery after the acute episode and was able to continue his activities in some measure, though painfully aware of the cardiac deficiency, and with periods of greater or less distress.

He became much interested in determining the cause of these periods of clinical distress and began to make daily recordings of weather change, of his state of well-being*(D)*; his breath-holding time*(C)*. This latter varied from less than thirty seconds on days of greatest discomfort, to more than sixty seconds when he "felt better." In Figure 6 his record is graphed for the month of February, 1944. The upper silhouetted curve is the daily maximal and minimal temperature*(A)*. This, it will be observed, varied from a maximum over 60° on the 26th, to a low of—5°F. on the 13th.

The subjective state is indicated in the curve "clinical condition*(D)* and there are clinical notes concerning S. G. of Chicago,*(E)* a mutual friend. Observe that by the 11th his subjective condition had declined and the breath-holding time had dropped abruptly *(1)*. This with the major decline in environmental temperatures from 55° to —5°F. By the 14th the decline in well-being was exaggerated. At this time S. G. became ill.

With warmer temperature H. I. felt better, and breath-holding time increased. A series of waves now followed in breath-holding time, in environmental temperature and in well-being. Finally, at the same time that the condition of H. I. became worse (25th) S. G. died*(2)* when environmental temperatures increased rapidly. Why? Because the anoxia associated with the passage of the cold wave had induced a relative acidosis, and blood pressure began to fall. This decline was accentuated with the succeeding warm weather. With this collapse and death in S. G., there was a distinct decline in the well-being of H. I. This would be a characteristically portentous situation for coronary thrombosis*(2)*.

H. I. died on February 18, 1945 (Fig. 7). Here a striking polar air wave, which sent temperatures down almost to zero, was effective in throwing a greater load on a damaged myocardium, and death promptly followed.

Environmental rhythms of this character are continually effective in initiating corresponding biochemical and biophysical rhythms, as the human organism seeks to adjust to the demands of the environment and it is this change in the organism from day to day which the allergist must evaluate in the varied symptomatic picture of his patient.

THE IMPLICATIONS FOR THE ALLERGIST

Quite apart from the day-by-day and seasonal change in reactivity of the organism to an established allergy a number of other phenomena must be considered as they become evident in the changing clinical picture.

With the shift in the blood mass from the periphery to the splanchnic area and vice versa, as the organism parries environmental impacts, sensitization of tissues will be effected.

In the first place, a skin that is active (vaso-dilitation) will present a different receptive situation than a skin that is inactive, if the allergen is by contact.

If the allergen is one that reaches the blood stream and is universally distributed, then the circulation of the allergen and the presumptive "degree" of sensitization of the tissues or organs will vary with the state of the splanchnic-peripheral balance. If, for instance, the skin vessels

are dilated while the splanchnic area is relatively poor in blood, the probability will be greater that the allergen will be absorbed in the peripheral area, endothelium, the coats of the vessel, and the connective tissues. Under such conditions, sensitization and later clinical response might be ac-

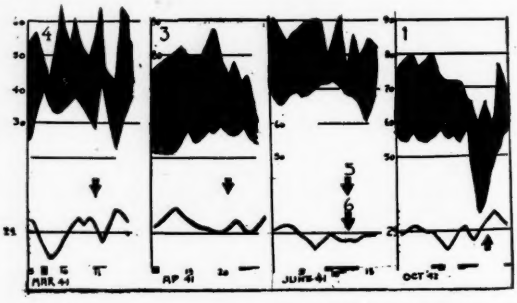

Fig. 8. Meteorogram to illustrate precipitation of jaundice following serum injection in the Beeson cases. Arrows date the association in Cases 1, 3, 4, 5, 6.

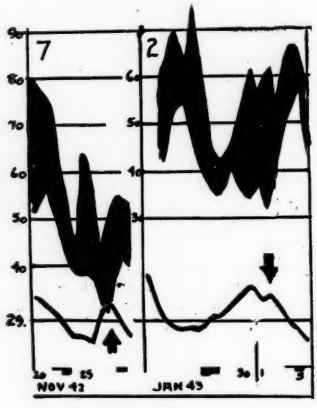

Fig. 9. Meteorogram to illustrate precipitation of jaundice following serum injection in the Beeson cases. Arrows date the association in Cases 2 and 7.

centuated in the peripheral tissues. If, on the other hand, the allergen enters the blood stream when the peripheral vessels are contracted, the opportunity for visceral sensitization will be much greater.

We have to consider another phenomenon that at first glance seems paradoxical. When patients suffering from hay fever and asthma are kept in air-conditioned (for temperature and humidity) and allergen-free chambers during the pollen season, they may still suffer severe asthmatic attacks with periods of major weather change. Dr. Tell Nelson has reported such an episode.[3]

I have shown that patients so confined still reveal a changing organic

rhythm that conforms to the environmental situation outside the conditioned chambers.

How can we explain such a paradox? The simplest would be the assumption that the sensitized tissues are actually more sensitive to change in the autonomic tone, irrespective of specific initiating factors. Or we might turn to a bacterial analogy. When bacteria enter the blood stream, they are rapidly picked up by the large blood filters and then rendered inocuous, or may vegetate for some time. If, now, a vascular shock occurs, bacteria so localized may again be thrown into the blood stream. We may have a related situation with the allergic phenomena. Assume that a reactive area exists in a joint membrane. The specific allergen may be inhaled or get into the blood stream in some other way. It might promptly be taken out by the liver and spleen. While held in the filters there would be no local manifestation. But if in the course of time an autonomic swing of sufficient degree would occur and with this, the "stored" allergen liberated, then a reaction might occur in the sensitized area even though the subject was in the air-conditioned chamber.

I shall illustrate an analogous situation using a series of case records of Beeson.[1] Beeson described jaundice occurring in army recruits from one to four months after the transfusion of blood or plasma, and dated seven cases when jaundice suddenly appeared.

I have prepared six small meteorograms of the time to illustrate the environmental situations. In these, the maximum and minimum daily temperatures are indicated in the black silhouetted field, and the case number is indicated. The barometric pressure is the heavy trace below—the precipitation by the black bars at the date line. The arrow points to the day of onset (Figs. 8 and 9).

The jaundice occurred when temperatures had declined as indicated:

Case 1. 80° to freezing.
Case 2. 75° to freezing.
Case 3. 88° to 56°.
Case 4. 65° to freezing.
Cases 5 and *6* (simultaneously!) 90° to 70°—at a period of severe rain for a week.
Case 7. 80° to freezing.

(For the seven cases, barometric pressure increased from 28.93" to 29.1" for the five days before the attack of jaundice.)

In these cases we are presumably not dealing with a specific sensitization; we are dealing with an altered state of the bile capillaries or of the parenchyma, and the altered state does not reach clinical significance until an environmental impact of magnitude so altered the biochemical state of the individual that local adjustment was inadequate and symptoms appeared.

Such changes in the reactive state are of importance in evaluating the allergic phenomena.

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PENICILLIN URTICARIA

MICHAEL ZELLER, M.D., F.A.C.A.
Chicago, Illinois

THE release of pencillin for civilian use has verified earlier reports on the frequency of urticaria resulting from penicillin therapy. Lyons[4] states that this complication developed in 5.7 per cent of 209 patients treated with penicillin. Anderson and Keefer[1] give its incidence as from 2 to 5 per cent. Criep[2] concluded that the urticaria is probably unrelated to penicillium spores. Feinberg[3] was unable to demonstrate penicillin sensitivity by means of skin tests of a group of patients showing positive skin reactions to extracts of penicillium spores. Lyons states that patients having penicillin urticaria do not develop urticaria following subsequent courses of penicillin, and that the period of sensitivity to penicillin is remarkably transient. He states further that cutaneous and ophthalmic tests during and after the reactive phase are negative. This is in direct variance with the findings of Criep, who obtained both positive intradermal skin tests and positive passive transfer in the presence of penicillin urticaria.

The following case coming under my observation seems worthy of record because of changes in the skin responses which may explain the apparent discrepancies in previous reports on penicillin urticaria:

CASE REPORT

A white woman, thirty-five years of age, entered the hospital May 25, 1945, with acute serofibrinous pleuritis. She gave no history of allergy, but stated that her maternal grandmother had asthma. Her past illnesses included chickenpox, mumps, and whooping cough. Blood studies on May 25 revealed 3,680,000 red blood cells, 21,900 white blood cells, 2 per cent eosinophils, and a sedimentation rate of 31. On June 19 there were 3,950,000 red blood cells, 7,600 white blood cells, 2 per cent eosinophils, and a sedimentation rate of 6. Thoracentesis disclosed a clear straw-colored fluid with occasional pneumococci and short-chain streptococci, 34 per cent polymorphonuclears, 16 per cent lymphocytes, and no eosinophils.

Penicillin was administered every three hours in doses of 25,000 units. Urticaria developed on June 19, appearing first on the face and neck and becoming generalized in a few hours. With each succeeding dose of penicillin the urticaria became more severe, and on June 20 the administration of penicillin was stopped. Severe urticaria persisted for three days more. On June 25, five days after the penicillin therapy was discontinued, the skin was again normal.

Studies were then conducted to determine the least amount of penicillin that would produce the urticaria; the component of penicillin responsible for the reaction; and the skin and ophthalmic responses to each component. The findings of these studies are presented in the tables.

Table I shows that during the reactive phase from June 19 to June 30 as little as 50 units of commercial penicillin sodium produced urticaria, whereas after this period the injection of increasingly high doses up to 20,000 units caused no reaction whatever. Significantly, also, injections

TABLE I. URTICARIAL RESPONSE TO VARIOUS DOSES OF PENICILLIN COMPONENTS*

Date	Penicillin component	Effect
June 20	5,000 units of commercial penicillin sodium.	Diffuse itch in 30 minutes, generalized urticaria in 1 hour, persisting to next day.
June 20	500 units of commercial penicillin sodium.	Diffuse itch in 25 minutes, generalized urticaria in 1 hour and 15 minutes, persisting 4 hours.
June 30	50 units of commercial penicillin sodium.	Diffuse itch in 25 minutes, generalized urticaria for 1 hour.
July 2	5 units of commercial penicillin sodium.	No effect.
July 3	416 units of crystalline penicillin sodium.	No effect.
July 4	832 units of crystalline penicillin sodium.	No effect.
July 5 a.m.	1,666 units of crystalline penicillin sodium.	No effect.
July 5 p.m.	3,200 units of crystalline penicillin sodium.	No effect.
July 6	2,000 units of commercial penicillin sodium.	No effect.
July 7	2,000 units of impurities of commercial penicillin sodium.**	No effect.
July 9	20,000 units of commercial penicillin sodium.	No effect.

*Crystalline penicillin sodium and impurities of commercial penicillin sodium made available through the courtesy of the Abbott Laboratories.
**Impurities of commercial penicillin sodium have not been identified.

TABLE II. IMMUNOLOGIC RESPONSE TO PENCILLIN COMPONENTS* AND PENICILLIN EXTRACT

Substance used	Intradermal tests	Control intradermal test	Ophthalmic test	Passive transfer
Penicillium extract, June 26, July 6, July 11	Neg.	Neg.	Not done	Not done
Commercial penicillin sodium (5,000 units per c.c.), June 26	Pos.	Neg.	Neg.	Pos.
Crystalline penicillin sodium (1,666 units per c.c.), July 6	Neg.	Neg.	Neg.	Not done
Impurities of commercial sodium penicillin (2,000 units per c.c.), July 7	Neg.	Neg.	Neg.	Not done
Commercial penicillin sodium (5,000 units per c.c.), July 9	Neg.	Neg.	Neg.	Neg.
Impurities of commercial sodium penicillin (2,000 units per c.c.), July 11	Neg.	Neg.	Not done	Neg.
Crystalline penicillin sodium (1,666 units per c.c.), July 11	Neg.	Neg.	Not done	Neg.

*Crystalline penicillin sodium and impurities of commercial penicillin sodium made available through the courtesy of the Abbott Laboratories.

of crystalline penicillin sodium and impurities of commercial penicillin sodium failed to produce urticaria after June 30. It is possible that if skin tests and passive transfer had been done with crystalline penicillin sodium and impurities of commercial penicillin sodium before June 30 the component responsible for the urticaria might have been determined.

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INHALATION OF TEN PER CENT CARBON DIOXIDE AND NINETY PER CENT OXYGEN PLUS 1:100 GLYCERINIZED EPINEPHRINE HYDROCHLORIDE FOR THE RELIEF OF ASTHMATIC ATTACKS

STEPHEN D. LOCKEY, M.D., F.A.C.A.
Lancaster, Pennsylvania

THE medical profession now recognizes that severe paroxysms of asthma and coughing are often relieved by the inhalation of 1:100 solution of suprarenalin hydrochloride.

It is also well known that 1:100 suprarenalin hydrochloride exerts a drying effect, often increases the cough reflex, and is also irritating to the mucous membranes.

To control the irritation of the mucous membranes following the use of the solution 1:100 suprarenalin hydrochloride, the use of glycerin in hot water orally was advocated immediately after the patient used this form of therapy for the relief of paroxysms of asthma and coughing. In 1943 the author[5] published a formula and method for the preparation of 1:100 glycerinized suprarenalin hydrochloride. Several large pharmaceutical houses now employ this formula or modifications of it, in the manufacture of glycerinized suprarenalin for oral inhalation. The formula is as follows:

Suprarenalin crystals	10.0 gms.
Sodium chloride	9.0 gms.
Chlorobutanol	5.0 gms.
Sodium bisulfite	0.9 gms.
Dilute HCl (10% U.S.P.)	20.0 c.c.
Glycerin	50.0 c.c.
Distilled water, to make	1,000.0 c.c.

Eight hundred fifty cubic centimeters of triple distilled water and 50 c.c. of glycerin are heated to boiling to remove the dissolved air. The heat is shut off, and the chlorobutanol and sodium chloride are added. The solution is cooled to room temperature, and the sodium bisulfite is added.

Ten grams of suprarenalin crystals are dissolved in 20 c.c. of 10% HCl and added immediately to the above solution.

The pH is then adjusted to 3.0 (a fluctuation from 2.9 to 3.1 is permissible). If necessary, a few drops of dilute sodium hydroxide solution may be used to bring the pH to 3.0. In case the HCl is a little weak, a small amount of normal HCl should be added.

Distilled water is added until the volume is exactly 1,000 c.c. The solution is then filtered and filled into bottles. (Avoid the use of metal apparatus in the preparation of material.)

The pure suprarenalin crystals used in making the 1:100 suprarenalin hydrochloride and also the technical data were freely furnished to the author by the Armour Laboratories, Chicago, Illinois.

Many tests were performed to insure that the glycerinized 1:100 suprarenalin solution retained its stability. Various batches were exposed to room temperature, stored in refrigerators, exposed to sun, stored in closets along with unglycerinized suprarenalin hydrochloride. The amount of discoloration present at the end of two, four, and six months was slightly less in the glycerinized material than in the unglycerinized.

It was also decided to vary the percentage of glycerin present in the formula. Various batches were made up that contained 5, 8, 11, and 15 per cent glycerin. These solutions were then tried in various vaporizers. It was found that if the open end of the vaporizer was held about four inches from a clear vertical piece of glass, the 5 and 8 per cent solutions produced the largest ring of vaporized solution on the glass.

The volume of solution expelled per minute from the end of the vaporizer was also measured. This was determined by attaching a saddle, hose and vaporizer to a small tank of compressed air, and then placing measured amounts of the 5, 8, 11, and 15 per cent glycerinized 1:100 suprarenalin hydrochloride in the vaporizer. The flow of oxygen through the hose was also controlled. As the percentage of glycerin per volume increases so the amount of solution vaporized per minute decreases.

A simple method and technique for the continuous inhalation of 1:100 glycerinized suprarenalin hydrochloride was published by the author in the article referred to above. The method is as follows: Use a small pressure tank of oxygen with the usual reducing valve to regulate the flow. An outflow tube is attached from the tank to a vaporizer, and oxygen is introduced at a flow sufficient to produce adequate vaporization. A flow of four to seven liters will vaporize 1 c.c. of solution in from three to ten minutes. When this method is used, the patient merely holds the nozzle of the vaporizer in his oral pharynx and breathes quietly. Very little additional effort is required (Fig. 1).

Richards, Barach and Cromwell stated the following advantages of this technique:

1. A larger amount of solution is brought into contact with the bronchial mucous membrane than is possible with the hand bulb.
2. This is done without effort on the part of the patient in a severe asthmatic state.
3. Solutions which are less irritating, and with milder bronchodilator action, are often effective in surpressing moderate asthmatic attacks when given by the continuous technique; whereas, they are ineffective when used with the hand spray. This is an important fact in patients who suffer from dryness and irritation of the mucous membrane of the tracheal bronchial tree, after the inhalation of 1:100 unglycerinized suprarenalin solution.

We all know that the following untoward effects often occur after the use of 1:100 suprarenalin hydrochloride, by either the continuous inhala-

tion method or the hand bulb vaporizer method: (1) dryness of the throat, (2) irritation of the throat, (3) nervousness, (4) palpitation, (5) nausea, (6) headache, (7) dizziness, (8) weakness, and (9) pallor. The appearance of these symptoms in individuals who use the hand bulb

Fig. 1. *A*, Oxygen, Carbon dioxide mixture; *B*, saddle for tank (Philadelphia Surgical Instrument Company, 1717 Samson Street, Philadelphia, Pa.); *C*, handle; *D*, flexible rubber hose; *E*, vaporizer.

vaporizer is often due to frequent inhalation of unsatisfactory amounts of the solution, and to the constricting effect of the drug on the mucous membrane, which in turn, brings on dryness and irritation. Dryness and irritation of the air passages occurs less frequently when the continuous inhalation therapy is used. Abramson arrived at similar conclusions in 1940, after he had treated a group of patients for a period of several years with 1:100 epinephrine containing glycerol. Untoward symptoms occur less frequently when the glycerinized 1:100 suprarenalin hydrochloride is used in sufficient amounts to provide relief.

Holinger, Basch, and Poacher[3] recently published a very fine paper

on the effect of carbon dioxide on the bronchial secretions, in which they make the following statements:

"Carbon dioxide may be considered an extremely efficient expectorant. It alone reaches the deeper, very obstructive type of secretion which must be frequently and efficiently drained to prevent serious types of permanent pulmonary or bronchial damage. It is apparent that the action of carbon dioxide is in part dependent on its ability to stimulate an actual resorption of secretions. However, its most important actions are to enforce deeper, more active respiratory movements as well as to liquefy the sputum and stimulate the cough reflex. By evacuating the more dependent bronchi, sputum otherwise inert is brought to a level from which it can be coughed out easily or removed more efficiently by direct suction through the bronchoscope.

"Examination of expectorated sputum following various periods of oxygen administration showed an increase in its content of organic and inorganic substances. The extent to which these factors had been increased suggested that the action of oxygen had been one of concentration of the sputum. This was confirmed by the bronchoscopic picture. The tracheobronchial mucosa was pale or even blanched in appearance following oxygen administration, and the measured viscosity of aspirated mucus had decidely increased over the usual measured viscosity of the aspirated mucus of the same patient without oxygen. A clinically important observation was the adherence of plaques of mucous to the bronchial walls, an observation never noted on the same patient without oxygen inhalations.

"The actions of gas inhalations are quite specific, and they grossly influence the physical and chemical qualities of both the expectorated and the bronchoscopically obtained sputum, as well as the character of the bronchial mucosa. Steam inhalation, or the inhalation of a high humidity atmosphere, results in the liquefaction of sputum. Carbon dioxide has an action quite similar to that of steam, but to a greater degree. And in addition, it increases the resorbing power of the bronchial mucosa; consequently it may be considered an extremely efficient expectorant."

Carbon dioxide 10 per cent may be used with 90 per cent oxygen in the pressure tank mentioned above, with the usual reducing valve to regulate the flow. A vaporizer containing 1:100 glycerinized suprarenalin hydrochloride is attached to a rubber outflow tube and vaporization of this material through the attached tube and vaporizer. The patient merely holds the nozzle of the vaporizer in his oral pharynx and breathes quietly.

This procedure has been employed by us twenty-eight times and the following effects have been observed:

1. Bronchodilator action takes place from the inhaled glycerinized 1:100 suprarenalin hydrochloride.
2. Dryness of the tracheobronchial tree is prevented by the use of glycerin in the solution. It also helps to raise the humidity of the inhaled air and vapor.
3. The resorbing power of the bronchial mucosa is increased.
4. The sputum is liquefied and the patient is able to expectorate more easily.
5. Long, tenacious, thick mucous plugs are often coughed up after the inhalation of 1:100 glycerinized suprarenalin by means of the carbon

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PARENTERAL USE OF BUTANEFRINE IN ASTHMA

A Comparison With Epinephrine

MILTON M. HARTMAN, M.D., F.A.C.A.

San Francisco, California

ASTHMA is always annoying and often incapacitating; therefore it behooves us to consider any addition to our armamentarium against this ailment, which at some time or another affects two per cent of our population. The author and his associates previously reported on the pharmacology and clinical use in asthma of a new sympathomimetic drug, ethylnorsuprarenin, also known as butanefrine. Chemically it is 1-(3, 4-dihydroxyphenyl)-2-amino-1-butanol. To recapitulate briefly, injected intramuscularly or subcutaneously in approximately twice the dosage employed with epinephrine, it gave equivalent relief in asthma. Butanefrine lacked the pressor effect of epinephrine; actually the diastolic pressure was moderately lowered, with a widening of the pulse pressure and slight acceleration of the heart rate. Butanefrine did not provoke nausea and vomiting, making it preferable for use in children. No angina was produced in patients with associated cardiac or hypertensive disease, making it preferable in this group. Finally, tremor and nervousness in general was encountered less with butanefrine than with epinephrine. The asthmatics studied were mainly uncomplicated "extrinsic" cases (from externally introduced allergens).

The purpose of this paper is to report further comparisons of the effects of butanefrine and epinephrine on asthmatics, this time separating them into two groups: those of extrinsic and reflex origin uncomplicated by infection, and those whose asthma was accompanied by definite bronchial infection. The latter included cases of both intrinsic and extrinsic origin.

FURTHER STUDIES BY INJECTION METHOD

In twenty-three more uncomplicated "extrinsic" asthmatics the clinical relief paralleled practically exactly that obtained with epinephrine; the ages of the patients ranged from four to fifty-nine years. In seventeen cases of "extrinsic" asthma complicated by bronchial infection that obtained relief from epinephrine, ten obtained the same relief, four less relief, and three none at all; the ages ranged from twelve to sixty years. In a group of twenty "intrinsic" cases (all with negative skin tests and with varying amounts of bronchial infection) one obtained more relief, twelve approximately the same relief, four cases less relief and three cases no relief. The ages of this last group ran from thirty-one to sixty-four years. Dosage employed was 1 mg. butanefrine per 45 Kg. (100 pounds) body weight, twice that of epinephrine. The subcutaneous route was employed. The same lack of angina and nausea was noted in these

TABLE I.

LUMEN-INCREASING EFFECT	EFFECT POSSESSED BY EPINEPHRINE	EFFECT POSSESSED BY BUTANEFRINE	RELATIVE IMPORTANCE OF EFFECT IN UNCOMPLICATED EXTRINSIC AND REFLEX ASTHMA	RELATIVE IMPORTANCE OF EFFECT IN ASTHMA WITH BRONCHIAL INFECTION
1. Relaxation of bronchiolar smooth muscle spasm	*	*	****	***
2. Lessening of vascular bed of mucosa through vasoconstriction	*	–	**	***
3. Lessening of mucosal edema by diminution of the arteriolar-venule pressure differential	*	–	**	**
4. Lessening of mucosal edema due to improved lymphatic drainage allowed by relaxation of bronchospasm	*	*	***	**
5. Lessening of secretion indirectly thru constriction of vessels supplying mucous glands and epithelium	*	–	*	***

cases as in the original report, and the same diminution of tremor and nervousness as compared with epinephrine.

MECHANISM OF ANTI-ASTHMATIC ACTION AND COMMENT

Leaving side actions out of the picture and confining our attention strictly to the relief of asthmatic respiration, it is apparent that whereas epinephrine and butanefrine are equally effective in the purely extrinsic (and reflex) asthmas, when the element of infection enters butanefrine becomes relatively less effective. The explanation of these facts becomes apparent when the mechanism of the bronchial-lumen-increasing actions of these two drugs are considered. The accompanying table needs no amplification. It can be seen that epinephrine, because of its added vasoconstrictor effect, has the balance tipped in its favor when infection is present but in uncomplicated cases this factor is negligible.

Because the vasoconstrictor action of epinephrine limits its own absorption, the effect is apt to be more prolonged than the effect of butanefrine, which does not limit its own absorption. However, the use of butanefrine is much safer for emergencies intravenously because of this lack of pressor effect. To delay the absorption of butanefrine and thus prolong its effect, five to ten per cent of epinephrine solution can be mixed right in the syringe with butanefrine for intramuscular or subcutaneous injection. Ultimately such measures for prolonging the action of epinephrine as suspension of the hydrochloride in gelatine or the base in oil will be tried with butanefrine.

USE OF BUTANEFRINE IN "CARDIAC" ASTHMA

During the course of these investigations butanefrine was tried on four cases of "cardiac" asthma. There were no adverse effects and only questionable beneficial ones. Administration of morphine, after no effects were apparent from the butanefrine, gave characteristic excellent relief of symptoms. Neither a cardiologist nor an allergist usually has much difficulty in distinguishing between cardiac (three per cent) and bronchial (ninety-seven per cent) asthma. However, a general practitioner frequently may be at a loss, and he is faced with a therapeutic Scylla and Charybdis. Although epinephrine benefits asthma it has an adverse effect upon cardiacs and hypertensives, particularly those with coronary artery disease. Morphine is of immense benefit in the cardiac cases but it is usually dangerous and sometimes fatal in bronchial asthma, since it inhibits bronchiolar peristalsis and the cough reflex, allowing patients to drown in their own secretions. With butanefrine at hand, however, one can obtain relief in bronchial asthma without endangering the cardio-vascular system. In other words, one does not have to take chances with a therapeutic trial when he is using butanefrine.

SUMMARY

1. Butanefrine 1:500 and epinephrine 1:1000 hypodermically are equally effective in relieving asthma of purely reflex and extrinsic origin in the absence of bronchial infection.

2. The effectiveness of butanefrine is relatively less when bronchial infection is present.

3. The vasoconstrictor effect of epinephrine which is lacking in butanefrine accounts for the greater effectiveness of epinephrine in infected cases.

4. Angina, nausea and pressor effects are entirely lacking with butanefrine. Tremor and nervousness occur less frequently and with less severity with butanefrine than with epinephrine.

5. Therapeutic trial in asthma which may be of cardiac origin is safe with butanefrine.

450 Sutter Street
San Francisco (8) California

REFERENCE

The Butanefrine used in these investigations was supplied through the courtesy of the Winthrop Chemical Company.

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An Unusual Case of Sulfathiazol Sensitivity of the Renal Type. Peters, John and Koven, A. J.: Ann. Allergy, 2:230, 1944.

Case report revealing anuria following the use of sulfathiazol, total 14 grams. No crystallization or tubular concretion was found on cystoscopy and ureteral irrigations. Authors believe this is true sensitivity, acting on the renal tissue.

AN UNUSUAL EFFECT OF AMINOPHYLLINE ON THE INTESTINAL TRACT

Case Report

MICHAEL ZELLER, M.D., F.A.C.A.
Chicago, Illinois

THE object of this case report is to record observations on the effects of aminophylline on the intestinal tract and to suggest that aminophylline may be useful in the diagnosis and treatment of the allergic bowel.

The patient was a woman forty-two years of age with a history of bronchial asthma and hay fever of fifteen years' duration, intestinal distention, attacks of nausea and vomiting for eighteen years, and frequent headaches. Appendectomy fifteen years ago and cholecystectomy a year later failed to relieve the abdominal symptoms. Two additional laparotomies in the last ten years, performed for intestinal obstruction, resulted in no relief of the intestinal symptoms except the acute episodes. Two of the patient's sisters had bronchial asthma. Skin tests of the patient revealed reactions to grass and ragweed pollens and to dust. In addition, ingestion tests disclosed sensitivity to a number of foods, manifested by abdominal distention and pain.

During the ragweed season of 1944 the patient developed asthma, for which aminophylline, grs. 7½, was given intravenously. Not only was the asthma relieved, but at the same time the abdominal distention, which fairly simulated a seven-month pregnancy, disappeared. On subsequent occasions aminophylline was injected for the relief of uncomplicated abdominal distention causing distressing pain and discomfort. Before the injection of the aminophylline, measurements of the abdominal circumference taken at the level of the umbilicus and the costal margin at the level of the eighth rib were 40 inches and 31.5 inches, respectively. Measurements taken ten minutes after the injection at the same levels were 36.5 inches and 30 inches, respectively, a difference of 3.5 inches at the umbilical level and 1.5 inches at the costal level. At the same time there was complete relief of the abdominal distention, pressure and pain. This effect was observed repeatedly on subsequent injections, but particularly during an episode when all symptoms of acute intestinal obstruction developed. The usual intubation, enemas, and other palliative measures failed to relieve the obstruction. The intravenous injection of aminophylline, grs. 7½, produced complete relief of the formidable picture of intestinal obstruction within ten minutes. Epinephrine given hypodermically and aminophylline given orally in doses as high as 25 grs. a day produced no relief of abdominal symptoms; in fact, aminophylline given orally in doses exceeding 8 grs. daily increased the abdominal cramps.

X-ray studies were undertaken to determine the site of action of the aminophylline. Flat scout films before the injection revealed an air-filled descending colon and caecum with outward convexity of the descending and ascending colon, the former measuring 3.5 cm. in width at the iliac crest. Five minutes after the intravenous injection of the aminophylline the descending and ascending colons were displaced medially with the convexity directed medially and the descending colon measuring 6 cm. at the iliac crest. One and a half hours after the ingestion of barium and before the injection of aminophylline, roentgenograms revealed a feathery structure of the jejunum with clumping of the ileum and outward convexity of the ascending colon. Five minutes after the intravenous injection of 7½ grs. of aminophylline, roentgenograms revealed rapid filling of the ascending colon with medial displacement and straightening of the convexity, and clumping of the ileum giving way to definite looping.

Roentgenograms made before and after the intravenous injection of aminophylline revealed no apparent effect on the gall bladder previously outlined with Priodex.

Askanazy[1] introduced the theobromine salts for the relief of cardiac dyspnea in 1895. Efron,[3] who in 1936 was the first to use aminophylline for the relief of bronchial asthma in the United States, stated that Van Leewen originally suggested the drug for this purpose in 1933.

Aminophylline has been used effectively also for the relief of biliary colic,[2,6] but I have been unable to find any previous report of an effect exerted by it on the gastro-intestinal tract except that of Huidobro, Montero, and Cuevas,[4] who observed that, in normal man, theophylline ethylenediamine acted like amyl nitrite on the jejuno-ileum, but less intensely and for a longer period of time.

The site of action of aminophylline in bronchial asthma has been variously ascribed to medullary stimulation of the respiratory center,[5] stimulation of the central nervous system, and its direct action on the bronchial musculature[7] producing relaxation of the contracted circular muscle. The mechanism of action in biliary colic has been thought to be the antispasmodic action of the drug on the musculature of the biliary tract[2,6] and perhaps, in addition, on the gall bladder. My own observations fail to reveal any action on the gall bladder.

The case reported herewith points to an antispasmodic effect of aminophylline on the allergic bowel indicated by the roentgenograms and clinical response. The collapse of the abdomen as noted by measurements is somewhat paradoxical for there was no passage of flatus at any time. It is suggested that the explanation may have been a redistribution of the gas in the bowel. The frequency of abdominal symptoms in the allergic individual is well known although their mimicry of the acute surgical abdomen is not always recognized. It is suggested that aminophylline administered intravenously may not only offer diagnostic differentiation under these circumstances but also relieve the allergic bowel.

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4753 Broadway

Editorial

THE FUTURE OF AMERICAN MEDICINE

Apart from a postwar labor civil war, one of the most serious problems confronting us and which involves both the medical profession and the public is the threatened enactment of the Wagner-Murray-Dingell Bills introduced into Congress May 24, 1945. Of The 185 pages of these bills, 183 are given to exhortation, propaganda, provisions, and benefits. The remaining two pages are devoted to assessing ten billion dollars annually for the single purpose of setting up a wholly socialistic device for the purpose of providing "Personal Health Services" for all Social Security beneficiaries and all of their dependents—110,000,000 people.

This unprecedented departure for alien collectivist control under the guise of true humanitarianism is truly more revolutionary and far-reaching than any proposals ever presented before in the United States Congress. As now proposed the bills form the basis for "Compulsory Health Insurance," which means state medicine. This political distribution of medical care if made a law would be the first important step in transforming a rapidly expanding Federal bureaucracy with totalitarian state control as its goal.

If enacted, these bills would make the Surgeon General of the Public Health Service a medical dictator, under the direction of the Administrator of the Social Security Board, a layman, to provide the services and with full authority to hire doctors, specialists, dentists, nurses, laboratory technicians, and establish rates of pay; establish fee schedules for physicians' and dentists' services; fix the qualifications for specialists; determine the number of individuals for whom any doctor or dentist may provide service; determine what hospitals or clinics may provide service for patients and under what conditions. There would be required a public record of the most intimate and sacred personal relationships of every patient. This information could be used by the curious and unscrupulous at will.

The over-all Social Security tax is to be eight per cent of wages up to $3,600, four per cent to be paid by the employer and four per cent by the employee. Self-employed are required to pay five per cent of "the market value" up to $3,600 of their services. The tax is five per cent for the state and local governments coming into the system, half being paid by the government unit and half by the employee. For Personal Health Services, three of the eight per cent tax, or approximately $3,142,000,000 a year, would be provided. However, this stupendous sum is to be supplemented from the General Revenue. All payments are to be made in cash. Payments are to be made in cash when appropriating funds for the construction of hospitals and health facilities, providing grants for public health services and for maternal and child health and welfare service, as well as for comprehensive public health assistance for

the needy and to nonprofit corporations and agencies engaged in research or in undergraduate or postgraduate professional education. Workers are to be reimbursed during periods of unemployment and temporary disability. Cash payments are also made to provide monthly retirement benefits for all male workers having reached the age of 65 and female workers having reached the age of 60. Widows, mothers, parents, and dependent children of workers will receive monthly benefits. Also widows, widowers, or heirs on the death of workers will receive "Lump Sum Payments." However, *no cash payments are made* when providing Personal Health Service for all Social Security beneficiaries and their dependents.

A positive appraisal of these provisions would make the Surgeon General of the United States Public Health Service the dispenser and in complete control of all health care and the final arbiter of the physical and mental well-being of the nation. The whole procedure is revolting to American Medicine—American doctors who have developed a procedure of widely distributed medical care, which is the most effective that has ever been provided for any comparable number of people anywhere at any time. More than 25 million people are now provided with needed protection through the Blue Cross. With the expansion of this physician-sponsored medical service and employer-employee group insurance, other tens of millions can also be furnished the same adequate care with easier payments of the cost.

The medical profession recognizes that war production concentration and the development of new methods has resulted in a woeful neglect of hospital construction and other physical facilities essential to best medical care. The members of the American Medical Association through the formal action of their Board of Trustees endorsed the granting of federal subsidy to eight state and local groups to make thorough surveys of hospitals and other medical surveys and to appraise the needs of the various communities respectively; and to supplement the resources of state and other local groups to be used for providing facilities here needed. Senator Hill of Alabama and Burton of Ohio introduced in the United States Senate, February 14, 1945, bill 191, which makes full provisions for all such needs. The American Medical profession endorses and will adequately support the passage of the Hill-Burton proposals.

The Wagner-Murray-Dingell bills would give to the Federal Agency full control of all labor and working conditions throughout the land. It would give authority to one man to continuously shift workers from area to area and state to state. When making a factual analysis of the Medical and Hospitalization provisions of the Wagner-Murray senate bill 1161, John M. Pratt of the National Physicians Committee for the Extension of Medical Service, comments, "For too long, a semi-complacent medical profession, too proud really to protest, too overworked and over-

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Progress in Allergy

PEDIATRIC ALLERGY
A Critical Review of Recent Literature

JEROME GLASER, M.D., F.A.A.P., F.A.C.A.*
Rochester, New York

DEVELOPMENT OF THE ALLERGIC CHILD

To the pediatrician perhaps the most fascinating facet of the study of allergy is the detection of evidence of the allergic state as early in life as possible. This is all the more true since in many instances because of our knowledge of the ascendants or siblings we know in advance which infants are most likely to develop allergic manifestations. Campbell[10], in the first paper of its kind, has reported with almost telegraphic brevity on the general subject of allergic manifestations of the newborn. His article embodies the results of a questionnaire sent to some six hundred of the leading obstetricians, allergists and pediatricians of North America and his own personal experience.

According to the answers obtained from this questionnaire, the following in the newborn should make one suspicious of potential allergy: Retro-auricular intertrigo; seborrhoea capitis with or without other evidence of seborrhoea; intestinal bleeding after feeding cow's milk; geographical tongue; visible peristaltic waves; intrauterine hiccough; infants with pyloric stenosis who continue to vomit after operation; excessive rubbing of the nose (the so-called "allergic salute"); excessive sneezing, especially if nasal smears show eosinophilia; excessive hunger on a formula which contains sufficient calories; allergic colic which must be differentiated from colic due to swallowed air; excessive reaction to silver nitrate drops; excessive reaction to ammoniated mercury ointment or other salves or oils used to prevent intertrigo; urticaria shortly after breast feeding which usually disappears before the next feeding; intolerance to orange juice and cod liver oil; unusual sensitivity to sugar; early excoriation of the buttocks; asthma especially in a breast-fed baby whose mother's scalp shows excessive dandruff; laryngospasm; glossitis; edema of feet and hands; unstable parentage; hypertrophy of the thymus; and lastly, an infant born of allergic parents.

There are doubtless many items in the above list which pediatricians will challenge. It would have been helpful had Campbell stated what he considered to be the duration of the newborn period. Most pediatricians, even those majoring in pediatric allergy, have not seen in the newborn many of the conditions enumerated above. In my own experience, retro-auricular intertrigo, which was described by Kugelmas[46] as an indication in early infancy of a potentially allergic child, has occurred chiefly as an indication of failure of the mother to cleanse properly behind the ears. When she was instructed as to the proper procedure for so doing, this sign of the potentially allergic child usually disappeared. In the instances in which it persisted it has indicated a tendency to seborrhoeic rather than to atopic dermatitis.

Visible peristaltic waves in the newborn period are so common that they may be considered physiological. However, the general impression is that infants with pyloric stenosis, whether or not they continue to vomit after operation, are potentially allergic children. It is not at all uncommon for infants with pyloric stenosis to vomit

*Pediatrician-in-Charge, the Pediatric Allergy Clinic of the Strong Memorial and Municipal Hospitals of the University of Rochester School of Medicine and Dentistry, and Physician-in-Charge of the Allergy Clinic of the Genesee Hospital, Rochester, New York.

postoperatively. This has been discussed by Faber and Davis[27] and it does not seem reasonable to consider such vomiting as additional evidence of potential allergy. The newborn infant who has asthma must be considered already an allergic child by virtue of this typical manifestation. The thought that unstable parentage predisposes to allergy in the offspring is interesting but needs further elaboration before it will be accepted by pediatric allergists.

An analysis of the history of 200 of Campbell's allergic children seen in later infancy and childhood showed that 25 per cent revealed allergic symptoms during the newborn period. He also reports very briefly twenty-four cases of allergy of the newborn in his own practice. In all instances, apparent cures resulted following the removal of offending allergens. These cases are particularly interesting:

Case 1.—A newborn infant whose older brother died of anaphylactic shock after his first breast feeding, presented similar symptoms when one drop of his mother's milk was placed on his tongue. The infant was promptly weaned. One month later he gave a four plus cutaneous reaction to human breast milk.

Case 2.—Another newborn infant on being placed at the breast on the second day of life went into a state of anaphylactic shock so severe that the head nurse felt it advisable to baptize him during the episode. He was resusciated by means of epinephrine hydrochloride and artificial respiration and the same occurred when he was given one drop of his mother's milk. He too was weaned forthwith and later reacted to human milk on skin testing.

Allergy to human milk is so rare and knowledge of it is so important it is hoped that eventually Campbell will report these cases in great detail.

Case 3.—A newborn infant who would develop eczema each time his mother received an inoculation for pollinosis. It is presumed, although Campbell does not say so, that the child was being breast fed at the time.

Case 4.—A newborn infant who developed eczema in the hospital which was later shown to be due to starch in the nurse's uniform.

Next to the detection of the potentially allergic infant, the most interesting privilege of the pediatrician is the study of the development of the allergic state as this infant develops. Clein[11] has reported a follow-up study of 100 allergic infants over a period of ten to fifteen years. All of these were observed in private practice. The test for allergy in every instance as the cause of symptoms was the clinical test: i. e., the disappearance of symptoms on removal of the offending allergen. Orange juice was found to be the single most important allergen producing initial allergic sensitization or shock. The "allergic tongue" (geographic tongue) as the first symptom of allergy was noted in three cases. In 98 per cent of the allergic infants the first allergic symptoms, as observed by Clein, were rash (eczema), vomiting (pyloric spasm); gastro-intestinal distress (more or less persistant colic, gas, diarrhea and constipation), asthma, perennial allergic rhinitis, allergic tongue, hay fever, and hives.

Ninety-eight per cent of the allergic infants developed major allergic symptoms in their first ten years. They occurred in this order: perennial allergic rhinitis, pollinosis and asthma. However, Clein observed that the first allergic symptoms have no relationship to the type of major allergy which will develop in later years. Most cases of major allergy developed before the age of six years; only 15 per cent in this series occurred after six years. While prophylactic treatment, which Clein discusses, advocated early and carried out thoroughly, did not prevent the development of major allergic symptoms as the child grew older, nevertheless Clein feels that it probably minimized the course of the disease and its complications.

Parents are frequently told that they should not worry about their children's allergy, since it will disappear as they grow older. Black[6] states that this does happen but is the exception rather than the rule, and that while all of us see persons who have had some form of allergic condition in earlier years which has been eventually lost, yet the number recovering spontaneously is small. In Black's esti-

mate it is not more than 10 per cent, which he rightly feels is too small a percentage to depend upon.

The fact that the incidence of asthma and hay fever is about twice as great in boys as in girls suggests that one of the hereditary factors upon which some cases of asthma and hay fever depend is transmitted as a sex-linked recessive factor. This observation suggested to Molholm[51] that there might be a relationship between asthma and hay fever in children and red-green color blindness, which is known to be dependent in all instances on a sex-linked recessive factor. One hundred sixty-five asthmatic male patients and 192 hay fever male patients, all thirteen years of age or less at the time of onset of symptoms, were tested for red-green color blindness by means of the Ishohara tests. The incidence of red-green color blindness in the whole group of patients was 8.4 per cent, which was about twice as great as the incidence of about 4 per cent in unselected males. This difference is statistically highly significant. The relationship thus found between red-green color blindness in men and some cases of asthma and hay fever in boys probably depends in part on a sex-linked recessive factor.

GENERAL CONSIDERATIONS

Pratt[54] briefly discussed the American approach to allergy in childhood and briefly reviewed the clinical method. He states that the chief difference between the United States and Great Britain is that in this country the immunological method of approach is particularly emphasized, whereas in Great Britain the therapeutic is more in favor.

Holt[41] warns that while skin tests are often of the greatest aid in the solution of an allergic problem, they must not be interpreted too literally. Before one can conclude that a positive reaction is clinically significant it must be confirmed by a clinical test. Holt points out the fact, which he states has received but scant attention in books on allergy, that summation of effects may occur when two allergens, neither of which produces much reaction alone, are encountered together.

Dighiero[21] has reported from Uruguay on 170 allergic infants. There were ninety cases of asthma, thirty of asthmatic bronchitis, seventeen of eczema and eleven of urticaria. The remainder were of various other conditions. Thirty-five per cent of the patients reacted to foods; 20 per cent reacted to both foods and inhalants; 15 per cent to inhalants exclusive of pollens; 2 per cent to pollens alone, and in 28 per cent of cases the allergen was not found on skin testing.

The perennial problem about what to do in the case of the allergic child who wishes to go to camp in the summer has been discussed by Glaser.[7] Because of the emergencies to which an allergic child is particularly susceptible, the primary consideration for such a camp is a resident physician, or at least a resident nurse with a physician readily available upon very short notice. Children on highly restricted diets should not be sent to camp even on diets which require the elimination of particular foods which may easily be omitted unless the child is known to be very co-operative. It is particularly important that the allergic child be immunized against tetanus by means of tetanus toxoid. The attention of the camp physician should be called to this fact so that the child if injured will not needlessly be given tetanus antitoxin. If for some reason the child is not actively immunized against tetanus the camp physician should be instructed not to use horse antitoxin but bovine antitoxin except in those children known to be sensitive to beef or milk, in which case a despeciated antitoxin should be used. If the child suffers from pollinosis it is advisable to send him to a pollen-free area if possible. The child should remain there until the pollen season is well over, even though this may require omitting the first week or two of school. All injection treatments which are given at home should be given in camp also but careful directions should be given the camp physician so that they will be properly administered.

The child should take to camp an adequate supply of the medications he customarily uses for his allergic difficulties. These should be clearly labeled so that the camp doctor will know exactly what is being used. The child should also take with him his own bedding, special pillows, blankets or blanket covers, a mattress or mattress cover if necessary. Unless he rooms by himself it will also be necessary to loan similar equipment to his roommate.

If the child is doing well, the effect of swimming upon his allergic condition is a problem to be judged in every individual case. Children with chronic atopic dermatitis may swim. The lesion should be protected with vaseline or some bland ointment. Children with eczematous skins are often quite sensitive to light and care should be taken to avoid sunburn. A coat of tan should be acquired very gradually. If tar ointments are used the skin is particularly sensitized to light and either special care must be used or an ointment not containing tar should be substituted.

In general, the child should avoid animals in camp as well as at home. In crafts and hobbies taught at camp he should avoid the preparing and mounting of animals with fur or feathers. It is better to interest the child in mineralogy or geology or the study of fossils or fish. He should not go on over-night hikes where he might have to sleep on the ground or in a barn. He should be taught to avoid poison ivy and should he be sensitive to this, prophylactic measures should be instituted before he goes to camp. Abnormally severe reactions to an insect sting may occur and if this happens the nature of the insect should be determined so that specific prophylactic therapy may be given if necessary.

ALTITUDE AND CLIMATE

It is a common belief that high altitudes favorably influence allergic diseases. The fact that this is not true is gradually being taught to us by our neighbors who practice in the great republic to the south. Mallén[48] has given a most enlightening discussion of the subject of allergy, including its relationship to altitude, in Mexico. Baker[2] has reported in even greater detail with particular reference to children. She states that evidence has been accumulated in Mexico City (altitude 7,325 feet) which indicates that allergic reactions are more common there than at lower altitudes. From this the author has deduced that (1) mountain sickness, the symptoms of which are the same as those of allergic reactions, may be explained on an allergic basis, and (2) the higher the altitude, the more allergy will be encountered. The symptoms of mountain sickness to which Baker refers as being similar to those of allergy, are nausea, vomiting, depression both mental and physical, and diarrhea. Baker states that her points are supported by case histories on 500 cases fifteen years of age or under. The cases were almost equally distributed as to sex and comprised 350 American or European and 150 Mexican patients.

Of the 500 individuals, 167 had either hives or urticaria, there being twenty-five cases of the latter. Of the 500 cases, 100 had diarrhea with accompanying vomiting in forty-eight cases. The most common offenders were eggs, milk, orange juice, and chocolate in the order named. The symptoms in most instances became acute within three weeks of arrival in Mexico City and cleared up on removing the offending foods from the diet. These reactions are definitely not due to some specific abnormality in Mexico City, as many children develop hives, diarrhea and vomiting from food products imported from the United States such as cod liver oil, canned beef, and evaporated or powdered milk. They clear up when a particular food is omitted from the diet or when the patient goes to a lower altitude where these foods may be taken. The author cites many cases illustrating this last point.

As an explanation for this fact it occurred to Baker that the anoxia experi-

enced in an altitude such as Mexico City may result in a greater absorption and accumulation of protein products than at lower levels. Low pressure is definitely the basic cause of mountain sickness and this definitely modifies various physiological functions. Baker states that she has been able to find only one reference in the literature available indicating an influence of altitude on allergic manifestations. This is the paper by Kopaczewski and Marczewski[43] on anaphylactic shock recording the induction of convulsions in guinea pigs sensitized to beef serum albumen one month previously. These animals together with normal controls were placed in a pneumatic caisson and the atmosphere depressed at a rate corresponding to a rise in the air of 1000 meters per minute until the equivalent of 10,000 meters was reached. At the latter figure all sensitized animals were in convulsions (with the exception of those which had gone into convulsions earlier) and a slow descent was made. At 6,000 meters (in three minutes) all the animals recovered, the only symptoms persisting being a lower temperature. Controls remained normal except for slight lowering of temperature.

Loss of weight characteristically accompanies the anoxia of high altitudes and the reasons for this have been assumed to be loss of appetite, restlessness, diarrhea, et cetera. In those coming to Mexico City a period of about two weeks is usually required in older children for the effect to accumulate and become manifest in symptoms. It is suggested that anoxia occurring at this altitude may result in a greater permeability of the gastro-intestinal tract to offending substances. Baker's recommendations are as follows:

Children with allergic reactions to food do well at this altitude if the following precautions are taken: (1) Avoid overloading on any one food; (2) not giving any one food more than once or twice a week; (3) avoid eggs, chocolate, too much cow's milk, wheat and orange juice; and (4) supplementing the diets with vitamins *A*, *D*, *B* complex, *C*, and calcium. Particular foods discovered to cause trouble must be at least temporarily omitted from the diet.

In Tel-Aviv, Palestine, Feiga and Rosenbaum[2], according to Unger[73] made meteorologic studies on three isolated dates when many children with chronic asthma developed severe attacks. There were no special changes in weather conditions on these three dates, although the authors point out the asthma may have been due to the sudden appearance of pollens in the air.

GASTRO-INTESTINAL ALLERGY

Abdominal pain due to food allergy has been discussed by Ratner[57] with his customary thoroughness and clarity. The fact that abdominal pain of allergic origin may be present without confirmatory evidence of a positive skin test may be explained by the fact that the gastro-intestinal tract is sensitized before the skin. He placed abdominal pain of allergic origin in three main categories: (1) Abdominal pain as a minor symptom, (2) recurrent abdominal pain, (3) severe abdominal pain simulating an allergic surgical condition of the abdomen. In the last category mentioned, Ratner pointed out that while the allergic reaction *per se* is reversible, yet the edema may pave the way for bacterial invasion and infection resulting in changes which are not reversible and which indicate surgical intervention. The importance of the therapeutic tests by the oral ingestion of ephedrine or atropin or the injection of adrenalin to relieve symptoms and clarify the diagnosis is mentioned. The reviewer, however, would like to point out that the failure of such a therapeutic test by no means rules out allergy. In this connection one need mention only how frequently adrenalin fails to relieve angioneurotic edema.

Ratner stated that the most concrete evidence of muscle spasm which may cause the abdominal pain is provided by the x-ray. The allergic abdominal pains may be initiated by (a) spasm of the gastro-intestinal smooth muscle, (b) wheal forma-

tion in the gastro-intestinal wall, (c) spasm of the small vessels of the gastro-intestinal wall, or (d) a combination of these factors.

In treatment the author referred to his so-called "allergenically denatured diet" for all patients with food allergies. This is based on his belief that heated albumen fractions are coagulated and therefore cannot act as allergens. However, some of the most interesting cases of allergic disorders in infants and children in the reviewer's practice have occurred with specific foods listed in this diet.

Brodribb[9] has reported a case of vomiting of allergic origin in an infant. The boy was a second child. He had an older sister who had no evidence of allergy, and there was no evidence of allergy in the parents. However, allergy was present in the families of all four grandparents. The mother drank milk liberally before and after the children were born. The patient reported upon was breast fed until he was five months of age. No cow's milk of any kind had been given previous to then. Starting at five months he was occasionally given a few teaspoons of diluted cow milk which had just been brought to a boil and cooled. This was invariably vomited except on the first two or three occasions when small quantities were taken. Further attempts were made with diluted or citrated milk at intervals of a few weeks and the vomiting became more severe. The child, however, had no eczema or other signs of allergy. He still vomited severely at eight months whenever cow's milk was tried and it was then noted that erythema developed on his neck, where it was moistened with the cow's milk. Patch tests with "humanized milk" (cow's milk dried at a temperature below 145° F.) on the infant's arm gave an intense erythema and urticarial wheal about ¾ inch in diameter in twenty minutes. A similar test with undiluted cow's milk after one hour gave a positive but less marked reaction.

The boy was then given a prepared milk called "Almata" which contains casein, egg yolk, and wheat flour proteins but no lactalbumin or lactoglobulin except perhaps minute traces. He did well on this, vomiting only occasionally and slightly and other foods were rapidly added and by nine and one half months he was weaned completely from the breast. On patch testing he did not react to Almata powder, pure casein, and pure lactalbumin (presumably but not definitely known to be of bovine origin). Patch tests with whey were slightly positive and with Seewa powder (whey dried below 145° F.) were positive but less positive than with humanized dried milk. Between nine and eleven months the positive patch tests to humanized dried milk became weaker and disappeared. Specific desensitization was carried out between ten and eleven months of age by the feeding of gradually increased amounts of whole milk. The author believes that the allergen responsible was lactalbumin or lactoglobulin, but since the source of the pure lactalbumin with which the child was tested was not certain, and since lactalbumin and lactoglobulin always occur together, it is difficult to say whether the specific desensitization by mouth was completely successful. With this the reviewer cannot agree as the author's report shows that the infant was well on his way to recovery as evidenced by the rapid decrease in the reaction to patch tests with humanized dried milk, even before oral desensitization was started.

A simple method for oral desensitization to food allergies is greatly to be desired. Urbach[74] has brought forward his propeptans as a means for doing this. Propeptans are derived from individual proteins by digestion with hydrochloric acid, pepsin and trypsin. They contain chiefly proteoses, but also peptones, simple peptides and amino-acids. A guinea pig highly allergized to egg white can be protected against usually lethal anaphylactic shock by a preliminary injection or feeding of egg propeptans. Other propeptans are totally inefficacious. In practice the specific propeptan is given on an empty stomach forty-five minutes before the next meal. In cases of extreme sensitivity, the patient may react to the propeptan itself and for this reason in such cases the patient should test the effect of the inges-

tion of one-tenth of the contents of the propeptan capsule. The specific propeptan must be given for each food to which the patient is allergic. If the symptoms persist and a nutritive allergy is still suspected, then carbohydrates, salt, and acid must be progressively eliminated from the diet. The average period of treatment with propeptans is between two and three weeks. The author refers to the case of a sixteen-months-old boy with asthma due to the ingestion of milk successfully treated with propeptan therapy.

The reviewer's experience with propeptans has been small but not satisfactory. It is unfortunate that this method has not had a more extensive trial by other investigators. Urbach's thorough work in this field and the importance of confirming or disaffirming his conclusions is so great that it is much to be regretted that others who have worked in this field have not published the results of their investigations, either affirmatively or negatively.[23]

ALLERGIC DERMATITIS

Two excellent reviews have appeared on the subject of eczema. These reviews do not overlap appreciably probably because the review of Epstein[25] is written from the viewpoint of the dermatologist and that of Rackemann[55] from the viewpoint of the internist and both from that of the allergist. Epstein's discussion of nomenclature is particularly interesting and his suggestion of the term "epidermitis" to replace the term "contact type dermatitis" merits careful consideration.

Generally speaking, allergists have paid little or no attention to the histopathology of the skin lesions with which they have dealt, and particularly is this true of the eczematoid dermatoses. It is for this reason that the presentation of this subject by Miller[60] at the first annual meeting of the American College of Allergists in June, 1944, was one of the highlights of the instructional courses given at that time. Miller stated that contact dermatitis differs from the other diseases by the type of vesicle, little or no acanthosis, and a mild superficial inflammatory reaction. Neurodermatitis (chronic atopic dermatitis) has a non-edematous regular acanthosis, thickening of the walls of the small arteries and a focal cellular reaction. Nummular eczema has the epidermis and cutis of neurodermatitis plus an intra-epidermic vesicle. Eczema is not a disease *sui generis* but is probably an expression of several diseases having similar findings. It differs (and here he refers to what pediatricians call acute atopic dermatitis) from the other three forms of eczematoid dermatitis (contact dermatitis, chronic atopic dermatitis, and nummular eczema) by an extensive cutis (corium) reaction involving the capillaries and an intense diffuse cellular reaction. There is also an irregular acanthosis most often with all signs of edema but sometimes with little or none. In all four groups of the disease the pathological process is superficial. In none of these is degeneration found and the cellular reaction never contains plasma, epithelioid or giant cells. There is no evidence of sequelae once the process subsides. In contact dermatitis, the epidermis plays a prominent role; in neurodermatitis the small arteries; in nummular eczema, the same as neurodermatitis plus a peculiar epidermic vesicle; in eczema, the cutis (corium) is the important feature, especially the involvement of the capillaries. This article, which fills a long-felt need by pediatric allergists, is beautifully illustrated and has to be read to be appreciated.

Cooke[13] has contributed a thought-provoking discussion of the subject of atopic dermatitis. He states: (1) "The term 'atopic dermatitis' is unfortunate in that it is used by some to indicate the hereditary feature as the word originally meant; by others to indicate the existence of an etiological significance of the wheal-reacting type of allergy and by many interchangeably as though the two were synonymous." (2) "The term 'atopic dermatitis' is inappropriate as it has come to imply that skin testing for immediate wheal reactions is a diagnostic procedure in eczema of the infantile type, which . . . it is not." (3) "Intradermal or scratch

tests must be discarded as diagnostic procedures in eczema, and the terms atopic dermatitis and neurodermatitis should be eliminated from our nomenclature." However, Cooke does not suggest an appropriate substitute term for "atopic dermatitis."

Most pediatricians agree with Hill[38] to the effect that "the term atopic dermatitis represents a useful and accurately descriptive nomenclature to apply to a well-defined clinical and immunological condition which is as much a distinct entity as diabetes is." Epstein[25] states: "The term 'atopic dermatitis' is a valuable addition because it is the only unmistakable term for this form of eczema. For this reason, it should be used, regardless whether one agrees with Coca's concept of atopy or not."

The old term, "infantile eczema," is too all-inclusive and too confusing. The term "atopic dermatitis" now connotes to the pediatrician a specific disease of infancy or its chronic form as it occurs in late infancy, and throughout the rest of childhood and sometimes almost the rest of life. To classify, for example, the most common form of contact dermatitis in infancy, the ammoniacal dermatitis of the diaper area and atopic dermatitis of the face in infancy, both under the term of "infantile eczema" is a step backwards. I would however agree to the elimination of the term "neurodermatitis" because this condition is now clearly recognized as a chronic form of atopic dermatitis and should be so designated. If this term is retained, it should apply only to such forms of this dermatitis as can be definitely shown not to be of allergic origin.[25]

As regards Cooke's second statement that intradermal and scratch tests must be discarded as diagnostic procedures in what most pediatricians now call "atopic eczema" is to highlight what most pediatric allergists realize, i. e., that the skin tests are related to the whole study of the patient in the same manner that the electrocardiogram is related to the complete study of the patient with heart disease, or blood sugar determination is related to the complete study of the patient with diabetes. Both the electrocardiogram in the case of the patient with the heart disease and the blood sugar determination in the case of the patient with diabetes may be left out of the study and the physician can still do well in diagnosing and treating the condition; he can do much better if he is privileged to do all the indicated laboratory procedures and in atopic dermatitis skin testing is just one of these procedures.

Cooke's point that a skin test in order to be diagnostic of the type of dermatitis must reproduce the type of dermatitis studied, is well taken. However, it can be reconciled with the wheal type of reaction induced in testing for atopic dermatitis. The most common reaction illustrating this which repeatedly occurs in skin testing in early infancy, is the skin test for egg white. The great majority of infants with atopic dermatitis react to egg white on scratch testing by the production of a wheal. These infants in most instances are also clinically sensitive to egg white. The type of reaction induced by skin testing is dependent both upon the degree of the sensitivity of the skin and the concentration of allergen brought into contact with the test site. If the skin is fairly sensitive and relatively enormous concentrations of allergen are brought into contact with the test site as occurs in ordinary scratch or intradermal tests, the reaction is overwhelming and is a wheal response; if the same sensitive infant is subjected to a clinical test in which he is fed a drop of egg yolk, the egg white proteins contained in and diluted by the lipoids of the yolk are further diluted by the tissue fluids and a minute amount of the egg white is brought by the blood into contact with the sensitive skin over a relatively long period of time as compared with the acute experiment of the dermal test and the more chronic form of reaction, the eczematous or atopic type of dermatitis appears in the infant's skin. Cooke's postulates are fulfilled in both instances because if the same child is fed a large amount of egg white, he does not break out with eczema but with hives; the acute experiment with the dermal test

is thus reproduced from within. Every pediatrician sees this happen repeatedly in his practice; in recent years not so often, since it is no longer a common practice, as formerly, to introduce egg yolk into the diet at the early age of three months. What has been described happens occasionally with other foods but less often and less dramatically than with egg.

The dermal test also has the use not commonly emphasized in assisting in the addition of foods to the diet of the allergic infant. If skin tests are done with a series of foods which one is considering adding to the infant's diet, it is not the part of wisdom to give those foods which react positively. One's chances of success are much greater if the negatively reacting foods are used. Probably the most common example of this is when cereal is to be added. Our cereal grains are biogenetically closely related, all being modified grass seeds. If one tests with wheat, rye, rice, oat and barley and obtains positive reactions to all but rice for example, it is only sensible to add rice as the infant's first cereal.

Strickler, Herman and Grumach-Fabian[68] studied gastric secretion in infantile eczema. The children varied in age from nine months to twelve years and comprised thirty-five patients with atopic dermatitis, four with seborrhoeic eczema, two with the ichthyotic variety and nine controls. The Ewald test meal was used. Free hydrochloric acid in the eczema group averaged 24.8 units and total acid 49.6 units. In the control group the free hydrochloric acid was 23.8 units and the total 43.3 units. The authors concluded that the values for infants with eczema failed to show any pronounced or consistent variation, either in free or total hydrochloric acid.

Physicians still continue to question the advisability of hospitalization of the eczematous child.[29] This question will always be in order but the situation as it stands at present has been thoroughly discussed in an original article by Epstein.[26] His contribution is significant not only because of the importance of the subject but because it is the first on this subject written by a dermatologist and also the first since the sulfonamide era began. He reports a series of 100 consecutive hospitalized cases of infantile eczema up to two years of age without deaths. The cases were classified as follows: atopic dermatitis, seborrheic dermatitis, contact dermatitis, and infectious eczema, chiefly intertrigo.

Sixty-four of the infants were admitted with uncomplicated eczema. Of these, fifteen or 23.4 per cent developed complications. However, all the complications but one occurred in infants with atopic dermatitis. The author believes that these occur chiefly as acute exacerbations of subclinical respiratory or gastro-intestinal allergy, and also that the susceptibility of the infant with atopic dermatitis to complications indicates a fundamental difference between this infant and the infant with the other types of eczematoid dermatoses.

Kaposi's varicelliform eruption (to be discussed subsequently) occurred as an admission complication in three cases. All survived. One patient developed a paralysis of one foot which was considered by the attending pediatrician to be possible evidence of poliomyelitis. Epstein felt, however, that in view of the fact that the virus of herpes simplex is a neurotrophic virus, the possibility exists that the paralysis might have been a consequence of that infection.

A much higher degree of eosinophilia is noted in atopic dermatitis as compared with nonatopic dermatitis. The average eosinophilia is 9.7 per cent which is just about twice as high as in the nonatopic dermatitis and about ten times as high as in other skin diseases used as controls. Anemia, however, was found just as often in the eczematoid dermatoses as in the other dermatoses of children.

The mortality of zero in the author's series is explained chiefly by the use of sulfonamides when indicated and by excellent nursing care. The author felt that since the advent of sulfonamides, death from eczema appears to have become an avoidable complication.

A valuable part of this paper is Epstein's discussion of sudden death in eczematous infants without apparent cause and the review of the constructive contribution by Davies[16], as well as the other literature relating to this subject. Epstein is inclined to favor the theory of Sulzburger[69] that phenol poisoning from tar in combination with interference with cutaneous respiration and the instability of the autonomic nervous system would explain satisfactorily the symptoms as well as the other circumstances of some of the acute deaths from eczema.

Despite the repeated warnings which have been issued regarding exposing an eczematous infant to a sibling or some other individual with a fresh vaccination, deaths from vaccinia in eczematous infants continue to occur. Such a case is reported in detail by Petersilge and Toomey.[52] This occurred in an eight-month-old white infant who had been eczematous since birth. A six-and-a-half-year-old sister had been vaccinated nine days before lesions appeared on the patient. There was a question as to whether the sister's lesions were dried with a wash cloth later used on the baby with eczema. Five days after the appearance of lesions on the skin, the baby was hospitalized with a generalized vaccinia. The white blood count was 13,500 with 39 per cent neutrophils and 17 per cent eosinophils. The Paul test was positive. The infant was treated with gentian violet, sulfadiazene, and human convalescent scarlet fever serum. However, she developed pneumonia and died fourteen days after the rash had appeared. Culture of the heart's blood showed a nonhemolytic streptococcus. Complete autopsy was done, and this showed patchy atelectasis, ulcerative laryngitis, ulcerative stomatitis, acute hyperplasia of the spleen, and generalized lymphadenopathy. There was moderate anemia. The kidneys, brain and spinal cord were completely negative.

Hershey and Smith[37] stated that generalized vaccinia in persons with eczema has been called "eczema vaccinatum." The incidence is reported as a complication of vaccination in about one in twenty thousand cases to one in ninety-six thousand and the case fatality rate is about twelve to thirty per cent. About two-thirds of the persons in whom this complication occurs have diseases of the skin and many are children with eczema. The incidence of eczema vaccinatum, however, must be much greater than is indicated by these figures as many cases occur which are mild and which are not reported and this probably happens even when some cases are severe. For example, in my own practice I have seen at least six of these and only two were severe enough to require hospitalization. None of these cases were reported in the literature. Many others have doubtless had the same experience.

The authors report a case of eczema vaccinatum in a twelve-month-old girl with an exacerbation of eczema. Her brother had been vaccinated twelve days before admission. The rash appeared ten days after admission to the hospital and three days after the development of the fever. The clinical diagnosis of generalized vaccinia was supported by the recovery of vaccine virus through animal inoculation and through demonstration of protective antibodies against vaccine virus in the patient's blood.

In conclusion, Hershey and Smith state that agents closely resembling the herpes simplex virus have recently been recovered from similar eruptions known as Kaposi's varicelliform eruption or pustulosis varioliformis acuta. These eruptions also occurred in patients with eczema and were formerly considered identical with eczema vaccinatum. A considerable number of patients have failed to yield either vaccinia or herpes virus, despite appropriate tests. This fact may be due to the localization of yet other viruses (as possibly chickenpox) in the areas of injured skin offered by these patients.

Interest in what is known as Kaposi's varicelliform eruption has been very great in the past couple of years. Barton and Brunsting[4], have provided a thorough review of the literature on the subject. They reported that atopic dermatitis was present in 80 per cent of the cases and 75 per cent of the cases were children under four

years of age. The mortality rate was 25 per cent, being much higher in children than in adults. A subsequent detailed discussion of this subject by Wenner[77] calling attention to the fact that this disease is probably in most instances a complication of eczema with the virus of herpes simplex was discussed in the first of these reviews.[32] Lynch[47] reported one case of varicelliform eruption in an infant two-and-a-half years of age who had a mild atopic dermatitis in the cubital areas. Three days before the onset of the child's illness the father suffered from herpes simplex of an eyelid accompanied by herpetic conjunctivitis. Another case occurred in a ten-month-old boy with a fairly generalized eczematous eruption of eight months' duration. The mother had herpes labialis simplex for two days before the eruption occurred. He also reported two cases in adults with eczema, one of whom had had herpes labialis two days before the onset and in the other there was no known history of exposure to herpes or vaccinia. In all four cases the presence of the herpetic virus was demonstrated. The author points out that the eruption originally termed "eczema herpetiforme" by Kaposi because it resembles herpes simplex actually is herpes simplex in an extensive form. Hence this disease should be called "eczema herpeticum" or spoken of as extensive herpes simplex complicating eczema (or other dermatosis).

The emphasis on Kaposi's varicelliform eruption (eczema herpeticum) in recent years has tended to overshadow the fact that eczema may be complicated by infections which are not of virus origin. In this connection the communication of Boisveit and Powers[7] is of significant interest. These authors point out that atopic dermatitis and streptococcal fever (rhinopharyngitis, cervical adenoiditis, low grade fever of several weeks' duration) are common diseases in the same period of life, the first three years.

In thirty-nine cases of secondarily infected eczema, hemolytic streptococci were recovered from twenty-six (66 per cent). From this small series it would appear that hemolytic streptococci are associated with infected eczema in about two-thirds of the cases. In four of the seventy-six cases of eczema admitted to the hospital there was present a lesion which went through the stages of papule, vesicule, pustule and crust and from these a herpes simplex-like virus was demonstrated by Wenner.[77] Of thirty-six clinically infected hospital patients whose skin cultures showed hemolytic streptococci, twenty-nine (77 per cent) also carried that organism in their rhinopharynx. Blood cultures were positive for hemolytic streptococci in three of the thirty-six infants with clinically infected eczema with skin cultures positive for that organism. It would appear that eczema in a child who has streptococcal fever or who is a carrier of hemolytic streptococci is likely to become infected.

Clinical differentiation between infected and noninfected eczema is not clear cut. Weeping is perhaps the most important single differential characteristic suggesting that an eczema is infected. Adenopathy, commonly present in eczema, is more marked when infection is present. Regardless of infection, a leukocytosis and an eosinophilia are often present in patients with eczema and are of little differential assistance.

For treating the hemolytic streptococcic infections the author used sulfonomides both orally and locally and concluded that there appears to be no support in clinical experience for oral administration of sulfonamides in these conditions. A skin level of approximately only one-half of that of the blood is obtained. A much higher concentration of the drug can be obtained locally by topical application. Five per cent sulfathiazole in white vaseline was found to be the most satisfactory preparation for local use. The authors observed that the healing of the infection was ameliorative but not curative of the eczema, and the infection, though not chronic, tends to recur because it is usually a part of streptococcal fever, a sub-chronic ailment.

Since the sulfonamide ointments were used generally for more than five days, the question of causing possible sensitization to sulfonamides was considered. At present the decision rests with the attending physician as to whether this risk is worth while. Holt[41] prefers sulfadiazene to sulfathiazole for local application because sensitization to sulfathiazole occurs much more easily. Boisvert and Powers[7] observe that it is possible that sulfonamide treatment of infected infantile ecema may be replaced by other local medication, as penicillin. In this connection I should like to suggest that tyrothricin should receive more consideration for use in topical application. Its bacterial spectrum is even broader than that of penicillin. Since it is not injectable it would appear preferable to use tyrothricin locally, reserving penicillin for those patients who require an antibiotic by injection. Although sensitization to penicillin apparently does not occur often, it does occur, and if tyrothricin will serve the purpose locally as well as penicillin it should be used for that purpose, thus sparing the patient the possibility of sensitization to penicillin in a condition which may be adequately treated by some other antibiotic.

A study of the clinical evaluation of soy bean food in the eczema of children has been made by Stoesser.[66] In this study, adequate environmental control and local treatment were instituted. Diet was started, apparently not on the basis of individual skin tests but as a type of elimination diet. A total of thirty-seven cases was studied. Twenty-nine patients accepted the soybean well. Undesirable looseness and frequency of the stools occurred in fourteen cases but was helped by the addition of a kaolin and pectate mixture. Of the twenty-nine cases who took the soybean milk well, the eczema disappeared in eighteen and was much improved in eleven. Twelve of the infants were found sensitive to milk. Of these, only five gave positive cutaneous tests to cow's milk protein. The remaining seventeen were considered to be sensitive to more than one food. However, after weeks of soybean food ingestion, they were able to tolerate better the other foods to which they had previously given clinical evidence of sensitivity.

A discussion on the nutritive value of soy beans has been published by Barnes and Maack.[3] This contains a detailed review of the literature but unfortunately omits reference to the work of Ruhrah[60,61] and of Hill and Stuart[39], so important to the pediatric allergist.

According to Holt[41], dehydrating procedures are unquestionably of value in treating infantile eczema. Restriction of the water intake is not advisable, but a marked improvement often follows the elimination of supplementary carbohydrate food. Top-milk formulas such as were popular in infant feeding some years ago are often helpful. Such high-fat formulas cause elimination of water from the body and loss of weight. Overfeeding is always to be avoided. The administration of potassium salts, a measure recommended a few years ago, is of little value unless accompanied by restriction of sodium chloride and at best makes but a slight contribution.

CONTACT TYPE DERMATITIS (EPIDERMITIS)

Plotz[53] has reported two cases of contact dermatitis in children ten months and six months of age respectively, due to hair lacquer used by the mothers. The ten-month-old child had been treated for "eczema" of the face for eight months without success. The dermatitis involved the forearms, especially the inner sides, right side of the cheeks and part of the forehead. No unexposed portions of the body were involved. The lesions in the six-month-old child involved the forearms, one cheek, most of the forehead and temples and the back of the neck. In both instances, patch tests with the mother's hair lacquer were strongly positive and the eruption disappeared when the mother discontinued this form of hair dressing.

PROGRESS IN ALLERGY

SINUSITIS

Birdsall[5] in his paper on the diagnosis and treatment of sinusitis in children has some most interesting remarks relating to mouth breathing. He stated that when true mouth breathing occurs, it is almost always a sign of sinusitis or of two other very rare conditions, congenital atresia of the posterior choane or nasopharyngeal tumor. The author distinguished between "mouth-breathing" and "mouth-openness" and stated that a very instructive experience may be easily enjoyed by visiting a children's ward at night. The proportion of children who are found sleeping with open mouths can be found to correspond very closely to the proportion whose age is below six years, the age at which the mandible begins to grow rapidly to accommodate the permanent teeth.

The "mouth-openness" of small children, misnamed "mouth-breathing," is commonly spontaneously cured by increase in the length of the body of the mandible. The angle of the mandible, which is 175° at birth, is reduced to 110° after puberty. Whether the patient is breathing through the nose or through the mouth may be easily determined if the observer will quietly approach with a cold spatula and hold it beneath the nostrils. The author makes this statement with which I believe no American pediatrician will agree: "I believe allergic nasal conditions to be very rare in children. I have very few notes of this occurrence in children and do not recall having recorded it except in hay fever." Birdsall states, in discussing the same subject, that the typical tissue response to the streptococcus, is the production of edema, not pus. Tonsilar inflammation is usually a result of sinusitis, as also are otitis media, conjunctivitis, and many types of deviation from normal behavior. The important result of inflammation of the nasal and sinus mucous membrane is a mechanical difficulty occasioned at the ostia by the swelling of the membrane in an inexpansible bony ring, which leads to a "sinus-block." The indication is to reduce edema of the ostia so as to permit nasal entry of air into the sinuses, and to facilitate the escape of the increased secretions. For this purpose he recommends the use of vasoconstrictors, especially neosynephrine one-quarter per cent, or ephedrine hydrochloride one-half per cent, in normal saline in Proetz displacement therapy.

McMahon[49] stated that the removal of tonsils and adenoids will cure 80 per cent of sinus infections in children. Polypi, deviated septi, and high-arched palates are predisposing causes in the remaining cases, with allergy and constitutional conditions as contributing factors. Extensive surgery in children is unwarranted except in emergencies such as exenteration of an infected sphenoid or ethnoid sinus because of coexistent optic neuritis. Chemotherapy has a definite place in the treatment of sinusitis. Local methods of treatment are detailed, particularly nasal irrigations.

ASTHMA

Invariably every parent of a child who has repeated attacks of bronchial asthma asks the question, "Doctor, will this damage my child's heart?" The answer to this, based on clinical experience, has been that the child will undoubtedly suffer no harm even though he may have repeated attacks of severe bronchial asthma. However, it remained for Derbes and Engelhardt[19] to subject this question to scientific investigation. Roentgen ray and electrocardiographic studies were made. A study of the heart size and contour of twelve asthmatic children ranging in age from five to fourteen years whose asthma varied in duration from one to nine years disclosed no abnormality fluoroscopically or on roentgenograms. They also studied[23] a series of seventeen children with an average age of 9.3 years; the youngest being five and the oldest fourteen years. The average duration of the asthma was 4.7 years with a minimum duration of fourteen months and a maximum of nine years. Detailed studies of the electrocardiograms were reported as normal. The authors felt that uncomplicated bronchial asthma in childhood is not a factor in heart disease. They state that this does not militate against the production of heart dis-

ease subsequent to pulmonary fibrosis, emphysema, bronchiectasis and other pulmonary complications seen in the chronic asthmatic state.

Mothers of asthmatic children who are thin and underweight frequently ask about the possibility of pulmonary tuberculosis in the asthmatic child. Black[6] said that he has seen few adults and no children in whom tuberculosis and asthma were coexistent. As far as children are concerned, the reviewer's experience confirms Black's observation.

Taylor[71] attempts to make a differential diagnosis between what is called "chronic pulmonary catarrh," a term introduced by Leys in 1927, and true allergic asthma. Of sixty-three patients under the age of fourteen years observed in the asthma clinic at the General Hospital in Birmingham, twelve had true allergic asthma. His criteria for true allergic asthma are: previous occurrence of infantile eczema, direct relationship between the attacks and exposure to foreign proteins, freedom from respiratory symptoms and signs between attacks, greater frequency in summer months, normal lungs physically and radiologically and response to adrenalin or ephedrine. The remaining fifty-one cases were examples of chronic pulmonary catarrh, their first diagnosis being variously asthma, recurrent bronchitis, or recurrent coughs and colds, et cetera. In a further group of thirty-eight children also under fourteen years of age seen in private practice, thirty-three showed evidence of recurrent catarrhal infections of the respiratory passages, only five being cases of true bronchial asthma.

The author stated that of the entire group of 101 children studied, 84 had associated underlying respiratory infections. Recurrent colds or upper respiratory catarrhs were followed by generalized pulmonary symptoms, as coughing, tight chest, wheeziness and more or less "asthma." In other cases persistence of cough was the most troublesome complaint. Most of the children seemed to show an increased susceptibility to respiratory infections or else had a chronic infection which was lighted up by unduly trivial circumstances such as changes in weather, exposure to cold winds, dampness, fog, rain, and all the attacks were more frequent during the winter and spring months. Taylor stated that Leys showed how the term "chronic pulmonary catarrh" usefully describes this common condition which numerous authorities have diagnosed under the terms fibrosis of the lungs, fibroid lungs, recurrent bronchitis, unresolved pneumonia, interstitial pneumonia, chronic bronchial pneumonia, peribronchitis, et cetera. Few necropsies have been recorded. Taylor stated that the differential diagnosis has to be made from true allergic asthma and from bronchiectasis and tuberculosis, both of which in the past have been commonly mistaken for chronic pulmonary catarrh. Treatment for chronic pulmonary catarrh is most satisfactory by climatic measures but breathing exercises are of value and will relieve the majority of cases.

It appears to me that what the author describes under the term chronic pulmonary catarrh embraces probably in most instances what we term "asthmatic bronchitis." However, the term doubtless includes a group of chronic pulmonary diseases not truly bronchial asthma. It is unfortunate that a study of the eosinophils in the nasal and bronchial secretions was not made in his cases. The presence of eosinophilia in such secretions places the burden of proof on the investigator who states that these conditions are not truly allergic in origin.

Dust bronchitis is a condition which may possibly be confused with persistent cough of allergic origin and possibly with bronchial asthma. Toomey and Petersilge[72] described an outbreak of noninfectious bronchitis occurring in an orphanage in Cleveland when the children played on a large field during fairly dry weather. During this time the surface of the field was covered with finely pulverized dust and the symptoms apparently arose from the inhalation of this material. This type of bronchitis has been previously noted in the Dust Bowl area. The average duration of the illness in each case was about two weeks. The principal symptom

was explosive, intractable, unproductive coughing, which was aggravated by excitement, deep breathing, or when lying on the back. The temperature often reached 38.4° C. (101° F.) but soon became normal when the child was put to bed. Whistling noises were heard in the lungs with loud bronchi at the bases. Roentgenograms showed only soft, patchy mottling with increased markings along the course of the bronchi. Treatment was symptomatic with sedatives and an expectorant cough mixture.

COMPLICATIONS OF ASTHMA

Francis[30] stated that subcutaneous emphysema complicating asthma is not common; only nineteen cases have been previously recorded in the literature. To these the author added two cases of his own. One was a girl thirteen years of age who had had bronchial asthma since early childhood. The episode complicated an attack of asthma following an upper respiratory infection. She was dyspneic and cyanotic with moderate swelling at the base of the neck due to subcutaneous emphysema. This was confirmed by a roentgenogram. The emphysema disappeared after ten days. The mechanism seems to be as follows: during asthma the bronchus is plugged because of spasm, edema and mucus. This acts as a valvular mechanism allowing the air to enter the alveolus, but hinders its exit during expiration. The intra-alveolar pressure is thus increased with rupture during a violent coughing spell. The free air then follows the reflections of the pleura, pericardium or perivascular tissue, to the posterior mediastinum, et cetera.

A case of bilateral spontaneous pneumothorax in a sixteen-year-old girl was described by Davidson and Brock.[15] She had had asthma since the age of three years. A left-sided spontaneous pneumothorax occurred which subsided but recurred four months later followed by a collapse of the right lung. A month later the roentgenogram showed a bilateral pneumothorax. Silver nitrate was introduced into both pleural cavities to promote adhesions.

A detailed discussion of the mechanism whereby air is found in extra-pulmonary spaces as a complication of bronchial asthma is given by Derbes, Engelhardt and Sodeman.[20]

TREATMENT OF ASTHMA

Holt[41] stated that the burning of asthma powders (stramonium leaves) occasionally produces satisfactory results. In asthmatic attacks in children which commonly follow upper respiratory infections the elimination of chronically infected pharyngeal tissue which cannot be treated surgically may be accomplished by radon. Where no such cause is evident and the respiratory infections are frequent and the asthmatic attacks severe, resort is sometimes had to the same treatment used for preventing recurrences of rheumatic fever; a small dose of sulfadiazene, 0.5 to 1.0 grams a day. That this procedure may be very useful is indicated by the report of Hodges[40] who used sulfadiazene as a prophylactic measure against respiratory disease in an army camp with very beneficial results. I have had a limited but highly favorable experience with this procedure in my own practice. Holt also states that Vitamin C may possibly be of some benefit in hay fever. My own experience cannot confirm this and recently published work rather definitely indicates that Vitamin C is of absolutely no value in pollinosis.[36,31]

The value of vaccine therapy in asthma is subject to perennial question. Stoesser[67] reported on a study of 214 children with allergic rhinitis or bronchial asthma or both which he followed for a period of two to four years. The children ranged in age up to sixteen years, although most were between six and ten years. In these patients the histories very clearly showed association of symptoms of acute respiratory infection with the allergic manifestations. Of the group there were fifty-nine who either did not respond to surgical procedures or who failed to give satisfactory reactions to the diagnostic allergenic extracts. In many of these chil-

dren, there was additional evidence in favor of infection as a primary cause of the attacks of allergic disease. There was no consistent response on testing with the bacterial allergens. Some patients with positive skin tests gave poor clinical results; some with negative tests gave good results. Eleven patients received autogenous vaccines with poor results. Stock vaccines were used in twenty-one cases with somewhat better results. The undenatured bacterial antigens of Krueger[45] were used in twenty-seven cases. Thirteen children showed remarkable improvement; nine gave a fairly satisfactory response and five were failures. Stoesser feels that the patients who improved could have had a specific response to this form of therapy; that autogenous vaccines may possibly have value if prepared from uncontaminated material secured through the bronchoscope as described by Crump[14] and that stock vaccines produce their results through nonspecific reactions.

Based on the theory that intrinsic allergy is of bacterial origin, Schonwald and Deppe[63] treated eighty-six cases of intrinsic bronchial asthma with a penicillin preparation. Forty-one patients were improved by this treatment. Eleven illustrative case histories were reported and these included three in children, five, seven and nine years of age respectively. The authors state that when their own preparation was used, subcutaneous treatments were given daily or every other day. Commercial penicillin was used in thirteen cases; 2500 units were given intramuscularly three times weekly. It is extremely difficult to understand how penicillin given in the doses mentioned by authors could have any beneficial effects, particularly in view of the rapid elimination of penicillin in the urine. Since their report, a paper reporting failure of penicillin in the treatment of intrinsic asthma has been recorded.[35]

Archibald[1] studied forty-five consecutive asthmatic children over periods ranging from six months to three years. The average age of the patient was eight years. Eighteen children received ethylene disulphonate alone; eighteen were given injections of distilled water alone and nine children received both. No children were treated who had responded well to the usual procedures. Benefit was obtained in a number of instances, both from the ethylene disulphonate and from the distilled water. The author concluded that the clinical effect of both was the same, being a form of physiological stimulation or nonspecific therapy.

Weiser [75,76] has reported on the treatment of bronchial asthma by means of breathing exercises. His series included twenty-nine children and twelve adults who suffered from bronchial asthma and in whom the usual methods of treatment such as specific and nonspecific desensitization had failed. The treatments discussed were intensive breathing exercises only. The aims were: to correct the physical deformities produced by the asthmatic attacks; to restore the elasticity of the thorax which is often fixed and distended in these cases; to develop and strengthen weak muscles, especially those respiratory muscles which were not already hypertrophied; and to prevent such secondary effects as chronic bronchitis, bronchiectasis, pulmonary fibrosis, cardiac hypertrophy and myocardial damage.

The author reports the details of the treatment which consists of massage and various forms of exercise. The progress of the patient is followed by frequent studies of vital capacity. The end results of treatment in general are very good. While the adults usually improve, they never attain the vital capacity of healthy people of corresponding age and physique. In the case of children this commonly occurs. The author states that the exercises which he describes are indicated in all cases of bronchial asthma showing a low vital capacity and cramped superficial breathing with poor chest expansion and little use of the diaphragm. They are contra-indicated in advanced bronchiectasis, severe emphysema, heart disease, pulmonary tuberculosis and febrile conditions. The method is usually unsuccessful if used for short periods only. The exercises should always be prescribed and supervised by a physician.

Pediatric allergists are familiar with the fact that children with respiratory allergies should not go about with bare heads and bare legs in cold weather. The question arose as to the effect which going about in this manner might have on normal children. This was answered in the *Journal of the American Medical Association*[54] as follows:

"Controlled experiments on this subject seem to be lacking. Some years ago it was stylish for children to be bare legged and hatless in cold weather under the theory that it would harden them against colds. The effects did not substantiate this idea, and certainly most pediatricians are agreed that young children at least should be properly protected against unnecessary exposure of legs or heads in cold weather. There is some reason to believe that chilling of certain portions of the skin may effect a decrease in resistance to infection, at least in some persons. The scientific evidence for the exact relationship between such chilling and susceptibility to colds, however, is tenuous. Insult to the human body by allowing a completely unnecessary chilling does not seem like a practice which thoughtful physicians can recommend, although the fact that enormous numbers of people do expose themselves freely to cold suggests that this is harmful only infrequently."

It is quite possible that these exceptions occur when the child is allergic, either clinically or subclinically.

URTICARIA

Derbes and Engelhardt[18] referring to the work of Sulzberger and Vaughn[70], who proved that inhalant substances may cause allergic dermatoses, reviewed the other literature on this subject and added two new cases of their own, one of whom was a boy eleven years of age who would develop asthma and urticaria when exposed to the fumes of fresh paint. It was particularly interesting that whereas the asthmatic attacks were over with in twenty-four hours, the urticaria persisted three or four days after the momentary stimulus.

ALLERGY OF THE CENTRAL SYSTEM

Rowe[58] has briefly reviewed the literature on this subject. These conditions usually but not necessarily occur in patients with a history of urticaria and especially of cutaneous swellings, as far as children are concerned. The author mentions case reports previously published by him of a boy with Jacksonian attacks due to egg allergy, of a girl with attacks of dizziness, irritability, generalized twitching and unconsciousness relieved by elimination from the diet of wheat, milk, egg and pepper; a boy with convulsive seizures and bronchial asthma due to pollen; and petit mal in a girl associated with nasal allergy due to animal emanations.

Clarke[12] describes the case of a child twenty-three months of age who had had convulsions for two months occurring several times a day. The child reacted on cutaneous testing to a number of foods and environmental factors. Recovery was complete on the elimination of these factors. The author states that he has many times seen infantile convulsions of allergic origin. He also reports two cases in children which had been diagnosed as idiopathic epilepsy and which responded to allergic therapy. In both instances other allergies were present. One behavior problem in a boy thirteen years of age with pollinosis responded to the elimination of several reacting foods.

HUMAN DANDER

The interesting work of Simon on the allergen in human dander has been previously reviewed.[32] Simon[64] states that the existence of allergic activity in the human dander may be regarded as having been established by previous investigators and confirmed by his present studies. Allergy to human dander is often associated with atopic dermatitis. Simon presents evidence that the allergen is not a constituent present in stratified squamous epidermis in general and that it does not have its

origin in accidental contamination of dander with suspended dust particles from the air. The fact that patients who are allergic to human dander give positive skin reactions also to the scales of seborrheic dermatitis, is in agreement with the clinical observations that this disease is often associated with excessive dander. The allergen may possibly occur in human dander as a result of some physiologic maturation process specific to the scalp epidermis or may have its origin in some microorganism living, but not always pathogenic, on the scalp.

DRUGS

In the previous review[32] demerol was discussed and it was stated that the properties of this new drug are such that it would doubtless have considerable value in asthma. It was further noted that no report of the dosage to be used in children had yet appeared in the American literature. Sprockhoff in Germany[65] recommends demerol in the croup of measles and diphtheria and pseudocroup. He believes that in some instances in these conditions by relaxing spasm tracheotomy may be avoided. While it is difficult to stop the cough in pertussis, its frequency and severity may be minimized. Demerol suppositories by night and demerol by mouth before meals will diminish the vomiting. He states that in general, vomiting is favorably influenced by demerol whether its origin is central or peripheral. The dosage advised by Sprockhoff is as follows: Infants, 2 to 4 gtts. by mouth, or a 25 mg. suppository or 0.10 to 0.20 c.c. subcutaneously; older children, 5 to 8 drops by mouth, or a 50 mg. suppository or 0.20 to 0.40 subcutaneously; larger children may receive 8 to 12 drops by mouth, or a 75 mg. suppository, or 0.50 c.c. to 0.80 c.c. subcutaneously. The solution of demerol used orally by Sprockhoff was a 5 per cent flavored aqueous solution not available in this country. Suppositories also are not available here.* The preparation he used subcutaneously is the same as that used in this country. Sprockhoff has observed that the younger the child, the more is the sedative effect.

In my personal experience, I have found demerol in combination with epinephrine hydrochloride very effective in the treatment of asthma in infants and children; more so, in my opinion, than in adults. Demerol is supplied in 2 c.c. vials containing 100 mg. each. I use the demerol and epinephrine hydrochloride solutions mixed together in the same syringe, a procedure commonly employed by others. A conservative hypodermic dose of demerol is 1.5 mg. per kgm. (or 0.015 c.c. of the solution per pound). The tolerance of infants for demerol is doubtless quite high. This was illustrated by a child with meningitis complicating an inoperable meningomyelocele. The child weighed 2280 gm. (5 pounds). For the relief of pain he was given 25 mg. of demerol (0.50 c.c.) by hypodermic without any apparent ill effects. This is a dosage somewhat in excess of 10 mg. per kgm. This was given without harm despite the fact that the intracranial pressure was increased, as evidenced by a bulging fontanelle, a condition in which demerol is said occasionally to produce very undesirable results.[34] Death occurred after the accidental administration of 220 mg. to a 6.5 kgm. (14 pounds) infant suffering from inoperable intestinal anomalies accompanied by obstruction, perforation and localized peritonitis. Within ten minutes after administration of the demerol, the child developed a patchy cyanosis and this was followed by what appeared to be respiratory arrest and death.

In infants weighing 3.6 kgm. (8 pounds) or more with severe colic not relieved by phenobarbital in the usual doses of 15, 30, or 45 mg. (¼, ½, or ¾ grains), I have frequently used one-half to three-quarters of a 50 mg. tablet orally with very good results and no undesirable side reactions. This is somewhat larger than the oral dosage recommended above by Sprockhoff.

*Personal communication from the Winthrop Chemical Co., New York, N. Y.

In the previous review[32], reference was made to the use of aminophyllin in suppositories as suggested by Dees[17] and it was suggested that if the patient is sensitive to chocolate (cocoa) it would be advisable to use some base besides cocoa butter for the suppositories. In response to inquiries as to what to use for a suppository base instead of cocoa butter, a suppository made of glycerinated gelatin (U.S.P.) may be used. In my own practice I have used as a suppository base propylene glycol monostearate,* and have found this very satisfactory.

PAREGORIC

Despite the fact that within recent years paregoric has been considered an unnecessarily complex mixture whose only virtue lies in the opium alkaloids which it contains, many pediatricians have continued to use paregoric for dry cough because of a feeling, based upon experience, that it is particularly useful in these conditions. An interesting study of the expectorant action of paregoric has been recorded by Boyd and MacLachlan.[8] They reviewed the history of paregoric and noted that Dr. Le Mort, a professor of chemistry at the Universtiy of Leyden from 1702 to 1718, is generally given credit for its origination. Under the name of "elixir asthmaticum" it became official in the London Pharmacopoeia of 1721. In the London Pharmacopoeia of 1746, the name was changed to "elixir paregoricum," a name which is still used as a synonym for paregoric. However, as a result of still further investigation into the history of the drug, the authors find it more logical to conclude that paregoric finally crystallized out of a welter of combinations of opium, dating back even to the Greeks, Romans, and Arabians, but especially to medical practice of the seventeenth to early nineteenth centuries.

By special methods of study, it was found that paregoric increased the output of respiratory tract fluid in various experimental animals and hence would probably have the same effect in man. What is most interesting is the fact that all the components of paregoric individually increase the output of respiratory tract fluid and when combined the ingredients have a more prolonged effect upon this output than that obtained by a summation of the individual ingredients. This was seen best in preparations of paregoric which had aged well over one year and which were of a dark brown color in contrast to the pale and light-brown color of nonaged preparations. Because of these experiments, the authors feel that they have provided laboratory evidence justifying the centuries-old use of paregoric in the treatment of dry, hacking coughs. Because of its marked expectorant action, paregoric is superior to morphine which probably has no expectorant action and to tincture of opium which has very little expectorant action.

IDIOSYNCRASY

Meyer[50] reports the case of a boy seven years old with impetigo. Sulfathiazole ointment was used locally and sulfadiazine orally. After four and one-half grams had been given in one and one-half days, lesions which were probably petechiae appeared in the boy's skin. A day and a half later when a total of seven and one-half grams had been administered, the urine became bloody and after a total of nine grams in three days, hematuria became marked and the boy was hospitalized. The hemoglobin was reported as 23 per cent, red blood cells as 1.43, white blood cells as 23,850 with 86 per cent polymorphonuclear leukocytes, and the platelets were reported as 20,000. The boy was treated with repeated transfusions and discharged nineteen days after admission. The author briefly reviews two similar cases which terminated fatally, one a patient of seventy-nine years with pneumonia and another a patient of sixty with a postoperative infected hip.

Koteen[44] reported the case of a boy five and a half years old with tonsillitis who was started on sulfadiazine on the second day of illness. He received 0.75 gm.

*Obtainable from the Goldschmidt Chemical Corp., 153 Waverly Place, N. Y.

every four hours for a total of nine grams, when the drug was discontinued because of absence of response. The next day the boy was hospitalized. On the third hospital day, the boy developed an acute morbilliform rash. He was treated with human convalescent scarlet fever serum without response. Penicillin therapy was then started. The throat symptoms and cervical lymphadenitis subsided but the boy's condition became critical. He was semi-conscious with a spiking fever and generalized edema. It seemed evident that the penicillin was not influencing the general course of the disease. On the eighth hospital day it was noted that the boy's blood did not clot in a test tube. At that time the prothrombin level was 54 per cent of normal and the platelet count 8,000. A diagnosis of sulfadiazine sensitivity with thrombocytopenea and severe toxic symptoms seemed justified. The sulfadiazine level was 2.3 mg. four days after the drug was discontinued. The boy improved on direct transfusion but on the eighteenth day developed granulocytopenia. He was given 2 c.c. of liver extract and 10 c.c. of pentnucleotide daily for eight days. Improvement was steady and he was discharged on the thirty-seventh hospital day, clinically well except for the persistence of hepatosplenomegaly. The history obtained after discharge indicated that on two previous occasions, the boy had had disagreeable reactions to sulfadiazine and sulfathiazole. This point would emphasize the importance of careful history taking in any child who is to receive sulfonamide therapy. The author emphasized also that hepatosphenomegaly rarely occurs after sulfonamide therapy. There is also mentioned the case of a boy five years of age who following sulfadiazine therapy developed a picture resembling the Waterhouse-Friedrichsen syndrome, with diffuse hemorrhage into the skin, shock and low platelet count. Necropsy showed massive hemorrhages into the adrenals.

A most unusual reaction to a single dose of 16 mg. (¼ gr.) of ephedrine sulphate in a boy 14 years of age is reported by Engelsher.[24] The history contained a note of extensive skin changes which appeared after one dose of ephedrine. For that reason epinephrine by hypo was used for relief. The statement in the first paragraph of the case report that the boy was receiving frequent injections of ephedrine is an error, as what was meant was epinephrine hydrochloride.* Since the boy had received no ephedrine for several years, the mother suggested the possibility of the loss of ephedrine allergy, in which case its administration might reduce the necessity of so many injections of epinephrine hydrochloride. This seemed reasonable, so the mother was instructed to give the boy a 16 mg. dose of ephedrine sulphate. Eight hours afterward, red, edematous, itching areas developed in various parts of the body and eighteen hours afterward marked angioneurotic edema of the lips had developed. Any contact with the affected areas produced pain. A few days later, the corners of the mouth became fissured and the acute manifestations began to subside. However, for many weeks later, ridging of the finger nails persisted with desquammation of the affected skin areas. It required several months for the skin and finger nails to return to normal. It is very interesting that in this case, local cutaneous tests with ephedrine sulphate were negative. The author emphasizes the rarity of such reactions to ephedrine, especially the ridging of the nails. He also emphasizes the fact which so often requires emphasis, that before prescribing, an inquiry as to drug sensitivity should be made, particularly in allergic individuals.

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Penicillin Urticaria

(Continued from Page 361)

In Table II are presented the skin responses which paralleled the clinical manifestations of urticaria. During the reactive phase, commercial penicillin sodium produced both urticaria and positive intradermal and positive passive transfer tests. After the reactive phase it had no effect. Attempts to obtain positive skin and ophthalmic tests and positive transfer with impurities of commercial penicillin sodium and crystalline penicillin sodium also failed after termination of the reactive phase. Penicillium extract injected intradermally caused no reaction in either the reactive or the non-reactive phase.

COMMENT

This case demonstrates that not only the penicillin urticaria but also the positive skin tests and positive passive transfer may be temporary. Whether or not the gradually diminished doses were responsible for the change or whether it occurred spontaneously cannot be stated. However, the results seem to warrant a trial of graduated doses of penicillin for densensitization in cases of severe penicillin urticaria.

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✶ *In Memoriam* ✶

R. C. LOWDERMILK

1872—1945

With the passing of Dr. R. C. Lowdermilk of Galena, Kansas, the medical profession has lost one of the first physicians in America to treat pollen hay fever and asthma with graduated doses of pollen extract. His work coincided with that of Dr. Karl K. Koessler, but was antedated by the English observers Noonan and Freeman.

The many people who were attracted to Doctor Lowdermilk as a physician, teacher or as a philosopher, have lost a friend who will be difficult to replace.

Doctor Lowdermilk was born in Asheville, North Carolina, in 1872. He was educated in a normal training school in Kansas. Afterwards he taught in the public schools until he studied medicine at the University Medical College of Kansas City, Missouri, graduating in 1898. He practiced general medicine until 1913, after which time he specialized in the treatment of hay fever and asthma. Patients came to him from far and near.

When I met Doctor Lowdermilk in about 1913, he was well along with the study of pollen therapy for the treatment of hay fever and asthma. At about that time he gave up his practice in Galena for a few months to work on the subject in the laboratories of the University of Kansas in Rosedale, Kansas. He had been attracted to the work on "Protein Sensitization" of Dr. Victor Vaughan of Ann Arbor, and was trying to repeat some of Vaughan's experiments by splitting the proteins of pollen, hoping to make them less toxic to human beings.

He told me at that time that he had completely cured himself of ragweed hay fever, by the injection of a suspension of ragweed pollen, but that he had nearly killed himself in doing so. He said that he had relieved a number of patients by the same method of treatment, but that he was afraid he had shortened his own life trying to stop the reactions caused by the pollen extract. He said he was satisfied that pollen therapy offered a therapeutic method by which hay fever might be cured, but that a method must be found for reducing the severity of the reactions produced. He said he had relieved himself by pollen injections to such an extent that he could actually gather ragweed pollen without displaying symptoms of hay fever.

Doctor Lowdermilk's work with pollen started in the summer of 1911. He was author of one original paper, "Hay Fever," published in the *Journal of the A.M.A.* in July, 1914. This, unfortunately, was his only publication. However, he took an active part in the work of the state and county medical societies, reading many papers on the subject of pollen therapy. The doctor had a well-equipped laboratory, collected his own pollens and made his own extracts. He also had a method of testing which was all his own. He would employ a platinum hypodermic needle provided with a metal adapter, which he had made himself. He would sterilize the needle in a flame, dip it into the extract, and then scratch the patient's skin with it. At the end of the scratch, he would force the needle into the skin, thus making, at the same time, a scratch and an intracutaneous test. He said that by observing the two ends of the scratch he could gain information which he could use in deciding whether or not the patient was sensitive to the extract.

Doctor Lowdermilk gave me some of his extracts at a very early date and requested me to help him with this study. This and my personal liking for the doctor was responsible for my going into the study of allergy, to the extent that I did in the early days. Also, I think that I should have discontinued this work at an early pe-

riod had it not been for Doctor Lowdermilk's repeatedly saying: "Bill, this is the only method of treatment for the disease which we have."

Doctor Lowdermilk had a very interesting appearance and personality. He was a large, rather fleshy, man with long, wavy white hair and a large, round face. He had a very winning smile, which was always in evidence when he was with his friends. He gave the appearance of being a very happy man, fully content with his work and what he was accomplishing by it. He was an interesting reader, philosopher and conversationalist, and was well acquainted with the studies of Einstein. He loved to discuss Einstein's work and views. It seems to me unfortunate that a larger number of people could not have been acquainted with Doctor Lowdermilk and gain by his stimulating influence. He chose to do his work in a small town. He enjoyed the simple life in the country and could not be enticed from it, except for short periods of time. Many of us who knew him well will miss him deeply.

WILLIAM WADDELL DUKE, M.D.

Asthmatic Attacks

(Continued from Page 365)

dioxide and oxygen pressure tank. The coughing up of these plugs of mucus relieves bronchial obstruction.

A small electric, mechanical aspirator can often be used after the above-mentioned procedure is employed. Long, tenacious plugs of mucus are often removed by the use of the mechanical aspirator.

SUMMARY

1. Suprarenalin hydrochloride, 1:100 glycerinized, plus 10 per cent carbon dioxide and 90 per cent oxygen used by means of the continuous inhalation method, will soon relieve severe attacks of asthma, increase the absorbing power of the bronchial mucosa, and help to liquefy sputum.

2. The carbon dioxide acts as an expectorant. This plus the bronchodilator action of the suprarenalin, and dryness preventive action of the glycerin in the solution helps the patient to cough up and expectorate mucus plugs.

60 N. West End Avenue

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News Items

Dr. G. Estrada de la Riva, Havana, Cuba, a member of the Editorial Staff of the ANNALS OF ALLERGY, registered for the Chicago instructional course.

The second annual meeting of the American Academy of Allergy will be held in Chicago, Illinois, at the Palmer House, December 10 and 11, 1945. Detailed information may be obtained by writing the secretary, Dr. Karl D. Figley, 316 Michigan Street, Toledo 2, Ohio.

There has been such a demand for bound volumes of the Progress in Allergy notes, which have appeared as comprehensive reviews of the literature on the various phases of allergy in the ANNALS, that the Editorial Board of the ANNALS is now having a limited number bound. Thus a very extensive bibliography and a brief review of the literature will be readily accessible to those interested in allergy as it applies to any particular specialty. An announcement will be made in the November-December issue concerning the price and when available.

Inquiries are being received from many men interested or specializing in allergy, who are being discharged from active service, for information concerning likely locations for the practice of allergy. It would be appreciated if anyone knowing of a vacancy or a demand for an allergist in a clinic or elsewhere would please notify the Secretary of the American College of Allergists, 401 La Salle Medical Building, Minneapolis 2, Minnesota. The College is attempting to conduct a Bureau for the purpose of helping to re-locate its members or any other physicians interested in allergy.

The editorial staff is establishing a new section in the ANNALS OF ALLERGY on Clinical Pathology. This will be under the direction of Dr. L. O. Dutton and will be limited to one or two pages. The discussions will be confined to well-recognized routine procedures, in an effort to stimulate more use of such in the study of the allergic individual. In the course of time the staff hopes to include a discussion of the theory and application of the more complicated tests. From time to time simple diagnostic procedures, as well as accepted therapeutic procedures which may have been overlooked, will be published.

Membership

Membership in the College so far is: Active Fellows 400; Associate fellows 67; Honorary Fellows 15; Corresponding Fellows 2. Another group will be considered for membership at the meeting of the Board of Regents to be held in Chicago, Illinois, Sunday, November 4, 2:30 p.m., at the Knickerbocker Hotel.

Additional Funds for Research in Allergy

Luzier's, Inc., Kansas City, Missouri, has made a grant of $1,500 to the College to be used for a research fellowship for one year. This will be known as the Luzier Grant for Fundamental Investigations in the Field of Dermatologic Allergy. The fellowship will be under the direction of Dr. Rudolf Baer, New York City, and Dr. Stephan Epstein, Marshfield, Wisconsin. The College is deeply grateful for the establishment of this Fellowship by Luzier's, Inc., in accepting such a worthy gift.

NEWS ITEMS

INTERNATIONAL ASSOCIATION OF ALLERGISTS

The International Association of Allergists, whose aims and purposes and plans were briefly announced in the July-August issue of the ANNALS has now been incorporated, without profit, and the Constitution and By-Laws adopted by the officers until the first meeting of the Association.

The general purposes of this Association are educational, scientific, and medical, and in particular for the advancement of the study, research, and clinical knowledge of allergy as it applies to the various specialties of medicine.

The active membership shall be open to physicians of good standing in the medical profession who are engaged as practitioners in the field of allergy. Membership in, or possession of the qualifications necessary for admission to, any organized allergy group which is a member of, or is affiliated with, or is accredited by, this Association, shall be taken, in the discretion of the Board of Regents, as sufficient proof of qualification as an allergist. Associate membership shall be open to physicians of good standing in the medical profession who apply allergy in their practice, and to any scientific student of the subject of allergy, and to any person engaged as a scientist or student of allied subjects. Honorary membership shall be limited to those persons having the qualifications of active or associate members and who shall be specially selected by the Board of Regents for outstanding and meritorious contributions in allergy and for eminence in their respective professions.

The general management of the affairs of this Association shall be vested in an Executive Committee composed of not less than three nor more than nine members, who, except the first Committee, shall be elected from and by the Board of Regents for a term of two years. The Executive Committee shall have the power to make and amend By-Laws for the government of this Association, subject to the approval of the Board of Regents.

The membership of this Association is divided into three classes: Active, Associate, and Honorary. The Board will provide appropriate certificates of membership and prescribe rules for their issuance. Candidates for Active membership shall be graduates of accredited medical schools and shall have done at least five years active practice in allergy and shall be not less than twenty-nine years of age at the time of application or nomination for membership. A written application form prescribed by the Board of Regents will be furnished candidates upon request. Supplemental information and evidence will be required as to the candidate's moral character and other qualifications, and he shall satisfy all other requirements imposed by the Articles and By-Laws of the Association. The Regents may require candidates to furnish and may consider among other things: hospital and academic appointments, personal acceptability to members in his territory, character, ethical standing, membership in medical societies, attendance at meetings of allergy groups, and membership in any such groups or other professional groups, and research or writings upon the subject of allergies and original investigations therein, and the quality and quantity of clinical reports with particular reference to the diagnostic and therapeutic summary in such matters.

Each nation and each of the self-governing dominions of the British commonwealth of which one or more of its nationals shall be active members of the Association, shall be entitled to one Regent and additional Regents, not exceeding a total of three Regents for any one nation or any of such dominions, to be selected or otherwise designated as follows: in any nation where there is no organized group of allergists which is a member of, or is affiliated with, or is accredited by, this Association, if there be only one active member of this Association, he shall, ipso facto, be the Regent for such nations, or if there be two or more such active members, they, or a majority of them, shall select the Regent; in nations where there is such a group of allergists, the Regent shall be selected by such a group; in nations where there are two or three of such groups, each group shall select a regent; and in nations where there are four or more such groups, the maximum number of three Regents shall be selected by the combined action of all such groups.

The Board of Regents shall have the power to appoint from among its own number an Executive Committee composed of not less than three nor more than nine members, which number shall include the officers of this Association, who ex officio shall be members of the Executive Committee. Between meetings of the Board of Regents, the Executive Committee may exercise all the powers of the Board, as permitted by law and in accordance with the policy of this Association and under the direction of the Board of Regents. The Board shall have the power to create

any additional committees and to prescribe their functions and duties, within the limitations of the Certificate of Incorporation and the By-Laws.

Regional or sectional meetings such as Pan-American and Pan-European Congresses or any other special meetings of the Association may be held at such times and places and under such conditions as the Board of Regents shall determine, either upon their own motion or upon the request of any twenty-five members; and all such meetings shall be open to all members. The officers shall consist of a president, vice president, secretary and treasurer and shall be elected from and by the Board of Regents for a two-year term and shall hold office until their successors have been elected and qualified. The officers shall, ipso facto, be members of the Executive Committee of this Association.

So far the Association has members from Argentina, Brazil, Uruguay, Chile, Guatemala, Mexico, Cuba, Australia, Canada, Great Britain, France, Switzerland, Russia, and the United States.

INSTRUCTIONAL COURSES AVAILABLE

Printed sets of the comprehensive outlines of lectures, including references, of the Fall graduate instructional courses presented by the College at Northwestern University, Chicago, Illinois, November 5th to 10th inclusive, are available for $6.00 a set. These are perforated to fit a standard ring book as formerly. Please mail orders to American College of Allergists, 401 LaSalle Medical Building, Minneapolis 2, Minnesota. Several lectures were stenotyped and copies of these will be included with the printed set.

Fundamentals of Allergy—Immunologic
FRED W. WITTICH, M.D., Minneapolis, Minn.

Fundamentals of Allergy—Physiologic
MAJOR HAROLD ABRAMSON (MC), Edgewood Arsenal, Md.

Experimental Allergy
PAUL R. CANNON, M.D., University of Chicago, Chicago, Illinois

Preparation of Pollen Extracts
GEORGE E. ROCKWELL, M.D., Milford, Ohio

Antigenicity of Proteins in Relation to Allergy
WILLIAM H. WELKER, Ph.D., University of Illinois, College of Medicine, Chicago, Illinois

Histopathology of the Allergic Reaction
BERNHARD STEINBERG, M.D., Toledo Hospital Institute of Medical Research, Toledo, Ohio

Materia Medica of Allergy and Pharmacology of Drugs Used in Allergy
CARL DRAGSTEDT, M.D., Northwestern University Medical School, Chicago, Illinois

Allergy of the Nose and Paranasal Sinuses—Perennial Allergic Rhinitis
FRENCH K. HANSEL, M.D., Washington University, St. Louis, Missouri

Botany of Hay Fever Plants
ROGER P. WODEHOUSE, Ph.D., Associate Director of Research in Allergy, Lederle Laboratories, Pearl River, New York

Ocular Allergy
A. D. RUEDEMANN, M.D., Cleveland Clinic, Cleveland, Ohio

Serum Disease
BRET RATNER, M.D., New York University College of Medicine, New York, New York

Allergy from Drug and Biological Products
JONATHAN FORMAN, M.D., Ohio State University Medical School, Columbus, Ohio

Reaction from Blood Transfusion
ANDREW IVY, M.D., Northwestern University Medical School, Chicago, Illinois

Bronchial Asthma (1st session)
LEON UNGER, M.D., Northwestern University Medical School, Chicago, Illinois.

Inhalation Therapy of Bronchial Asthma (2nd session)
ALVAN L. BARACH, M.D., Columbia University College of Physicians and Surgeons, New York, New York

Dermatologic Allergy—Atopic Dermatitis (1st session)
LOUIS R. BRUNSTING, M.D., Mayo Clinic, Rochester, Minnesota

Dermatologic Allergy—Urticaria (2nd session)
RUDOLF L. BAER, M.D., New York Post Graduate Medical School of Columbia University, New York, New York

Dermatologic Allergy—Contact Dermatitis (3rd session)
LOUIS SCHWARTZ, M.D., Medical Director, Chief Dermatoses Section, U. S. Public Health Service, Bethesda, Maryland

Pediatric Allergy—The Differential Diagnosis of Bronchial Asthma in Infants and Children (1st session)
JEROME GLASER, M.D., University of Rochester Medical School, Rochester, New York

Pediatric Allergy—Status Asthmaticus (2nd session)
JOSEPH R. WISEMAN, M.D., Syracuse University, Syracuse, New York

Pediatric Allergy—Respiratory Pollen Allergy in Children (3rd session)
M. MURRAY PESHKIN, M.D., New York, New York
Pediatric Allergy—Dermatologic Allergy in Children (4th session)
JOHN H. MITCHELL, M.D., Ohio State University Medical School, Columbus, Ohio
Allergy of the Central Nervous System—Migraine (1st session)
FOSTER KENNEDY, M.D., Cornell University Medical College, New York, New York
Allergy of the Central Nervous System—Ménière's Disease (2nd session)
BAYARD T. HORTON, Mayo Clinic, Rochester, Minnesota
Physical Allergy
CECIL KOHN, M.D., Kansas City, Missouri
Allergic Bronchitis and Bronchiectasis
J. WARRICK THOMAS, M.D., Vaughan Memorial Clinic, Richmond, Virginia
Clinical Use of Histamine
BAYARD T. HORTON, M.D., Mayo Clinic, Rochester, Minnesota
Diagnosis of Hay Fever
HARRY L. ROGERS, M.D., Jefferson Medical College, Philadelphia, Pennsylvania
Treatment of Hay Fever
HARRY L. ROGERS, M.D., Jefferson Medical College, Philadelphia, Pennsylvania
Gastro-intestinal Allergy
ORVAL R. WITHERS, M.D., University of Kansas School of Medicine, Kansas City, Missouri
Miscellaneous Allergies—Agranulocytosis
THERON RANDOLPH, M.D., Northwestern University Medical School, Chicago, Illinois
Mold Allergy
HOMER E. PRINCE, M.D., Baylor University, Houston, Texas
Less Common Manifestations of Allergy—Epilepsy, Loeffler's Syndrome, Joint Allergy, Purpura and Genito-Urinary Allergy
J. WARRICK THOMAS, M.D., Vaughan Memorial Clinic, Richmond, Virginia

The Conjunctival Test

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The Future of American Medicine

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burdened with war responsibilities to give adequate consideration to basic problems, has contented itself with the sophistry "It can't happen here."

"It is happening—now. Wartime fervor and preoccupation and wartime confusion are being used to obscure the true meaning of the moves. The issue is being forced. The settlement will be final. Doctors—informed—understanding—unified—can be the deciding factor in this final determination."

This issue must be decided by the voter of the United States. Please take time out to talk or write to your senator and congressman and indicate that political domination of medical progress will precipitate a medical revolution.

F. W. W.